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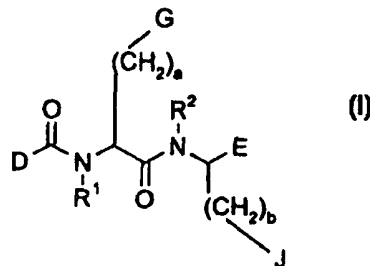
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(54) Title: **COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES**

(57) Abstract

Compounds of peptide mimetic nature having general formula (I), wherein a and b are independently 1 or 2, R¹ and R² are independently H or C₁-alkyl, G and J are independently, inter alia, aromats, and D and E are independently several different groups, are growth hormone secretagogous with improved bioavailability.



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COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES

FIELD OF INVENTION

5

The present invention relates to novel compounds, compositions containing them, and their use for treating medical disorders resulting from a deficiency in growth hormone.

10 BACKGROUND OF THE INVENTION

Growth hormone is a hormone which stimulates growth of all tissues capable of growing. In addition, growth hormone is known to have a number of effects on metabolic processes, e.g., stimulation of protein synthesis and free fatty acid
15 mobilisation and to cause a switch in energy metabolism from carbohydrate to fatty acid metabolism. Deficiency in growth hormone can result in a number of severe medical disorders, e.g., dwarfism.

Growth hormone is released from the pituitary. The release is under tight control of
20 a number of hormones and neurotransmitters either directly or indirectly. Growth hormone release can be stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin. In both cases the hormones are released from the hypothalamus but their action is mediated primarily via specific receptors located in the pituitary. Other compounds which stimulate the release of growth hormone from
25 the pituitary have also been described. For example arginine, L-3,4-dihydroxyphenylalanine (L-Dopa), glucagon, vasopressin, PACAP (pituitary adenylyl cyclase activating peptide), muscarinic receptor agonists and a synthetic hexapeptide, GHRP (growth hormone releasing peptide) release endogenous growth hormone either by a direct effect on the pituitary or by affecting the release
30 of GHRH and/or somatostatin from the hypothalamus.

In disorders or conditions where increased levels of growth hormone is desired, the protein nature of growth hormone makes anything but parent . ral administration non-viable. Furthermore, other directly acting natural secretagogues, e.g., GHRH and PACAP, are longer polypeptides for which reason parenteral administration is
5 preferred.

The use of certain compounds for increasing the levels of growth hormone in mammals has previously been proposed, e.g. in EP 18 072, EP 83 864, WO 89/07110, WO 89/01711, WO 89/10933, WO 88/9780, WO 83/02272, WO
10 91/18016, WO 92/01711, WO 93/04081, WO 9517422, WO 9517423 and WO 9514666.

The composition of growth hormone releasing compounds is important for their growth hormone releasing potency as well as their bioavailability. It is therefore the
15 object of the present invention to provide compounds of peptide mimetic nature with growth hormone releasing properties which have improved properties relative to known compounds of this type.

SUMMARY OF THE INVENTION

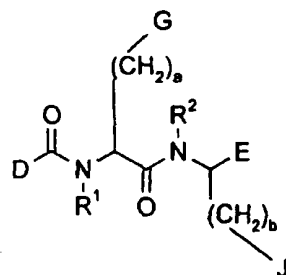
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In accordance with the present invention there is provided compounds which act directly on the pituitary cells under normal experimental conditions in vitro to release growth hormone therefrom.

25 These growth hormone releasing compounds can be utilized in vitro as unique research tools for understanding, inter alia, how growth hormone secretion is regulated at the pituitary level.

Moreover, the growth hormone releasing compounds of the present invention can
30 also be administered in vivo to increase growth hormone release.

Accordingly, the present invention relates to a compound of the general formula I



formula I

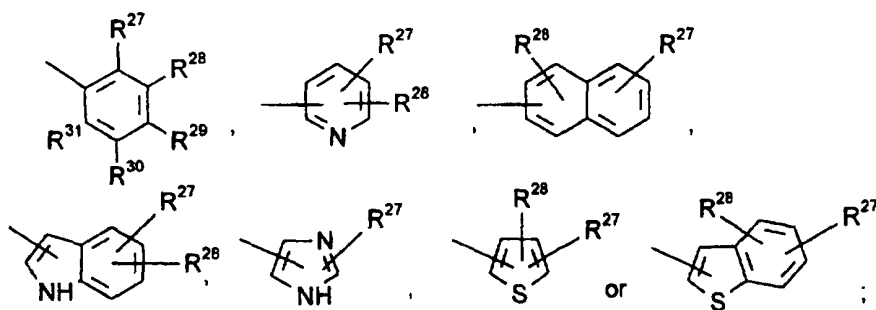
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wherein

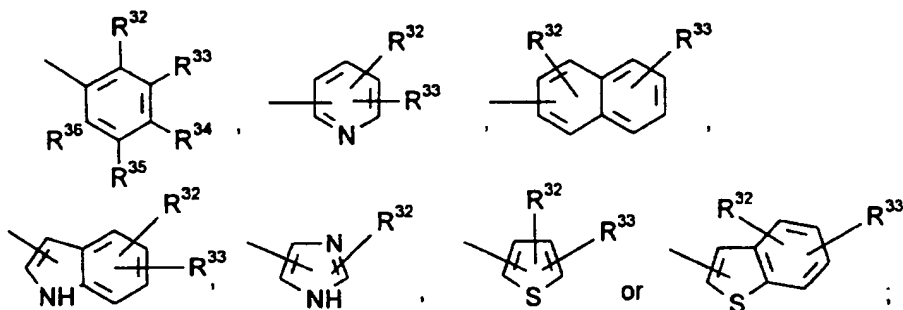
- 10 R^1 and R^2 are independently hydrogen, or
 C_{1-6} -alkyl optionally substituted with aryl;

a and b are independently 1 or 2;

- 15 G is hydrogen, $-O-(CH_2)_k-R^{27}$,



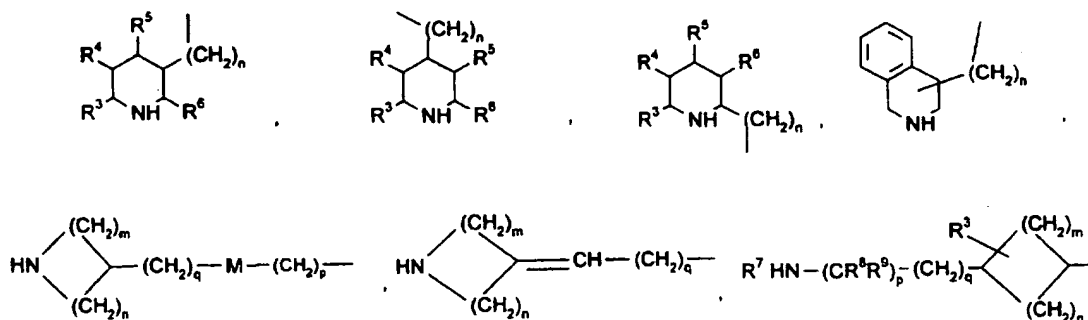
J is hydrogen, $-O-(CH_2)_l-R^{32}$,



wherein R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵ and R³⁶ independently are hydrogen, halogen, aryl, C₁₋₆-alkyl or C₁₋₆-alkoxy;

5 k and l are independently 0, 1 or 2;

D is



15

wherein R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ are independently hydrogen or C₁₋₆-alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

n , m and q are independently 0, 1, 2, or 3;

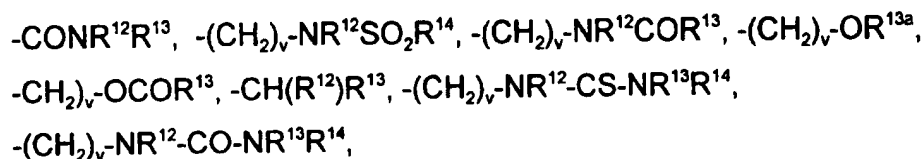
p is 0 or 1;

20 M is $-CR^{11}=CR^{11a}-$, aryl, $-O-$, or $-S-$;

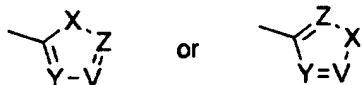
R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with aryl;

with the proviso that at least one of R³, R⁴, R⁵ and R⁶ is different from hydrogen,

when E is



5



wherein

X is $-\text{N}(\text{R}^{15})-$, $-\text{O}-$ or $-\text{S}-$,

10 V is $-\text{C}(\text{R}^{16})=$ or $-\text{N}=$,

Y is $-\text{C}(\text{R}^{17})=$ or $-\text{N}=$,

Z is $-\text{C}(\text{R}^{18})=$ or $-\text{N}=$,

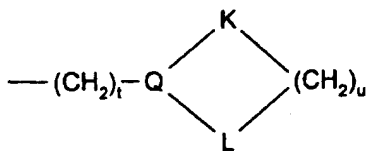
R^{15} is hydrogen or C_{1-6} -alkyl optionally substituted with aryl,

15 R^{16} , R^{17} and R^{18} independently are hydrogen, $-\text{COOR}^{19}$, $-\text{CONR}^{20}\text{R}^{21}$, $-(\text{CH}_2)_w\text{NR}^{20}\text{R}^{21}$, $-(\text{CH}_2)_w\text{OR}^{19}$, $-(\text{CH}_2)_w\text{R}^{19}$ or halogen;

R^{12} , R^{13} , R^{19} , R^{20} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, $-\text{CONR}^{22}\text{R}^{23}$, $-\text{N}(\text{R}^{22})\text{R}^{23}$, $-\text{CF}_3$, hydroxyl, C_{1-6} -alkoxy, C_{1-6} -

20 alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl,

or R^{13} is



25 wherein

Q is $-\text{CH}<$ or $-\text{N}<$,

K and L are independently $-\text{CH}_2-$, $-\text{CO}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{26}-$ or a valence bond,

where R^{26} is hydrogen or C_{1-6} -alkyl;

t and u are independently 0, 1, 2, 3 or 4;

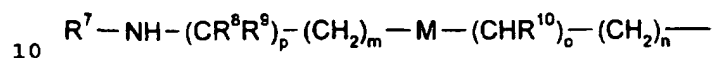
R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆-alkyl;

5 v and w are independently 0, 1, 2 or 3;

D is



wherein R⁷, R⁸, R⁹ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

15 R⁷ and R⁸ or R⁷ and R⁹ or R⁸ and R⁹ optionally forming -(CH₂)_i-U-(CH₂)_j-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

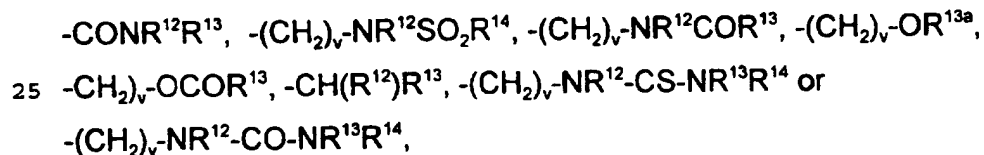
n and m are independently 0, 1, 2, or 3;

o and p are independently 0 or 1;

M is -CR¹¹=CR^{11a}-, aryl, -O-, or -S- ;

20 R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with aryl,

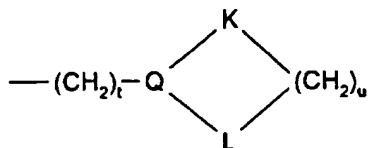
when E is



wherein

30 R¹² and R¹³ independently are hydrogen or C₁₋₆-alkyl optionally substituted with halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyloxy or aryl;

or R¹³ is



wherein

5 Q is -CH< or -N< ,

K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond,
where R²⁶ is hydrogen or C₁₋₆ alkyl;

t and u are independently 0, 1, 2, 3 or 4;

R^{13a} is C₁₋₆ alkyl substituted with aryl;

10 R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆ alkyl;

v and w are independently 0, 1, 2 or 3;

15 or a pharmaceutically acceptable salt thereof, and the compounds of formula I
comprise any optical isomers thereof, in the form of separated, pure or partially
purified optical isomers or racemic mixtures thereof.

In the compound of the above formula I D is preferably

20 3-(1-aminoethyl)phenyl, 4-amino-4-ethylhex-1-enyl, (1E)-2-(azetidin-3-yl)ethenyl,
piperidin-4-ylidenyl,

2-methylpiperidin-4-yl, 2-methylpiperidin-3-yl, 2-methylpiperidin-5-yl,

(1,2,3,4-tetrahydroisoquinolin-1-yl)methyl, 4-aminocyclohexyl,

2-piperidylmethoxymethyl, 4-piperidyloxymethyl,

25 2-(2-amino-2-methylpropyl)cyclopropyl, (((2R)-pyrrolidin-2-yl)methoxy)methyl,

(1E)-4-amino-1-benzyl-4-methylpent-1-enyl, (1E)-4-amino-4-methylpent-1-enyl,

(2-amino-2-methylpropoxy)methyl, (2S)-(2-pyrrolidinyl)methoxymethyl, (2R)-(2-

pyrrolidinyl)methoxymethyl, (1E)-4-amino-2,4-dimethylpent-1-enyl, (1E)-4-methyl-

4-(methylamino)pent-1-enyl, (1Z)-4-amino-4-methylpent-1-enyl,

(1E)-4-((2R)-2-hydroxypropylamino)-4-methylpent-1-enyl,
 (2-aminobutoxy)methyl, 3-(1-aminoethyl)phenyl, 3-aminomethylphenyl, 3-(1-
 amino-1-methylethyl)phenyl, 2-(1-amino cyclopropyl)ethenyl, 3-(1-
 aminocyclobutyl)-1-propenyl, 3-(1-aminocyclopropyl)-1-propenyl or 2-(1-amino
 5 cyclobutyl)ethenyl.

In the compound of the above formula I E is preferably methylcarbamoyl,
 ethylcarbamoyl, N,N-dimethylcarbamoyl,
 2-methoxyethylcarbamoyl, (2S)-2-hydroxypropylcarbamoyl,
 10 (2R)-2-hydroxypropylcarbamoyl, (cyclopropylmethyl)carbamoyl, (2-(acetoxymethylpropyl)carbamoyl, phenylethylcarbamoyl, 4-pyridylcarbamoyl,
 (3-acetoxypentyl)carbamoyl, (3-hydroxypropyl)carbamoyl,
 methylsulfonylaminomethyl, ((tetrahydrofuran-2-yl)methyl)carbamoyl, 3-
 cyclopropylthioureido, N-methyl-N-(methylsulfonylamino)methyl, (2,2,2-
 15 trifluoroethyl)carbamoyl, cyclopropylcarbamoyl,
 ((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl,
 3-methyl-1,2,4-oxadiazol-5-yl, methylsulfonylaminomethyl, 2,2-dimethyl-3-
 hydroxypropylcarbamoyl, 2-(1-methylpyrrolidine-2-yl)ethylcarbamoyl, N-methyl-N-
 (3-(dimethylamino)propyl)carbamoyl, N-(N,N-dimethylcarbamoyl)-N-
 20 methylcarbamoyl, N-(carbamoylmethyl)carbamoyl or 3-cyclopropylthioureido.

In the compound of the above formula I G is preferably
 2-naphthyl, 1-naphthyl, 2-benzyloxy, biphenyl-4-yl or 3-benzo[b]thiophenyl, 4-
 methoxyphenyl, 2,3,4,5,6-pentafluorophenyl.

25

In the compound of the above formula I J is preferably
 phenyl, 2-fluorophenyl, 4-fluorophenyl, 4-iodophenyl, 3,4-difluorophenyl
 2-thienyl, 4-methoxyphenyl, 2,3,4,5,6-pentafluorophenyl, 2-naphthyl or 1-
 naphthyl.

30

In the compound of the above formula I R¹ is preferably

hydrogen, methyl or ethyl.

More preferably R¹ is hydrogen, or methyl.

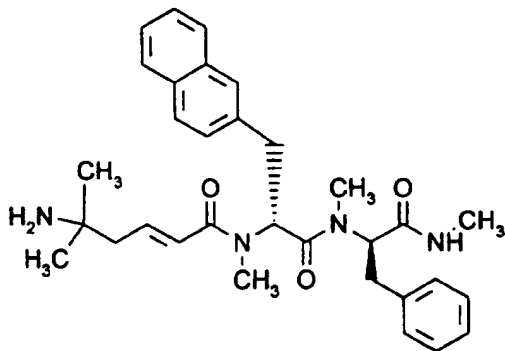
- 5 In the compound of the above formula I R² is preferably hydrogen, methyl or ethyl.

In the compound of the above formula I a is preferably 1.

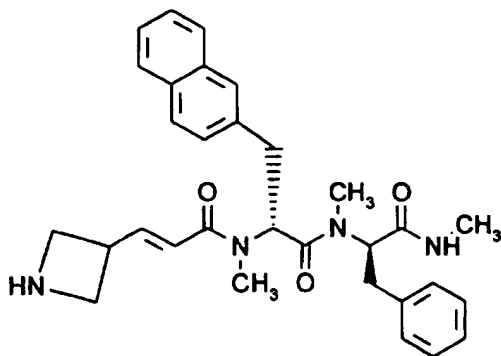
- 10 In the compound of the above formula I b is preferably 1.

Preferred compounds of the invention are:

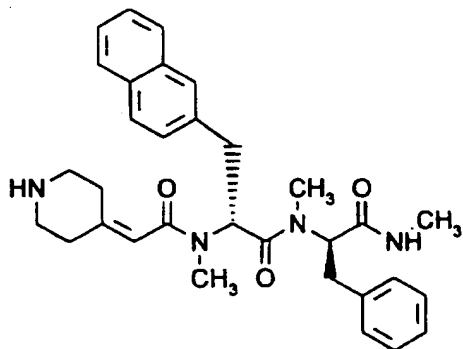
- 15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



- 20 (2E)-3-(3-Azetidinyl)acrylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

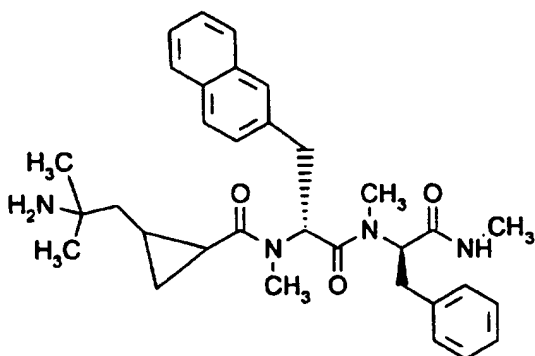


2-(Piperidin-4-ylidene)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



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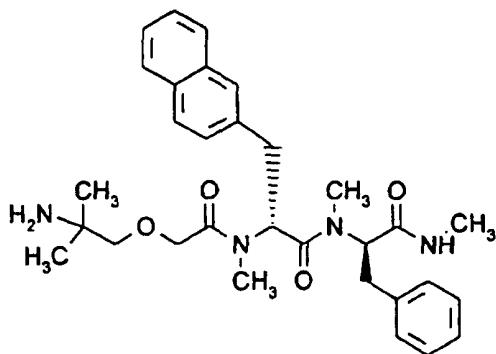
2-(2-Amino-2-methylpropyl)cyclopropanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



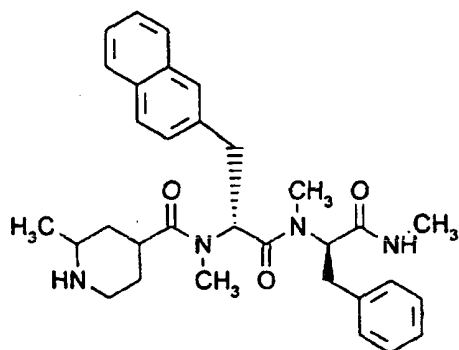
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2-(2-Amino-2-methylpropoxy)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

11

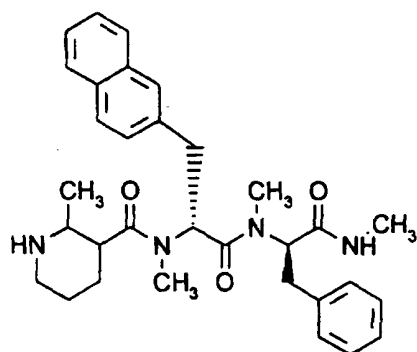


2-Methylpiperidine-4-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



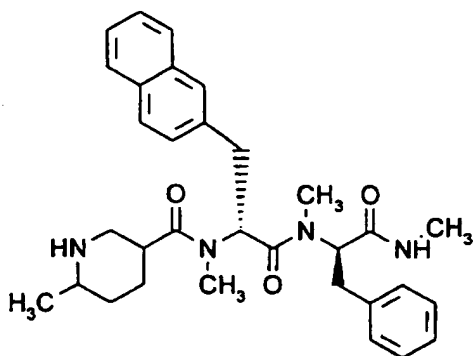
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2-Methylpiperidine-3-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

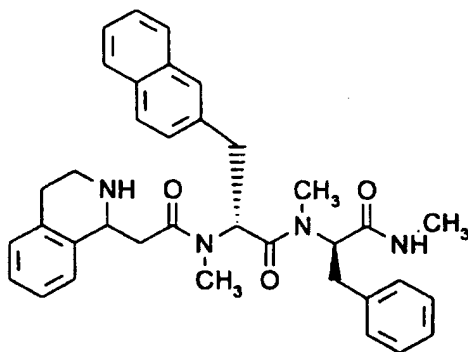


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2-Methylpiperidin -5-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

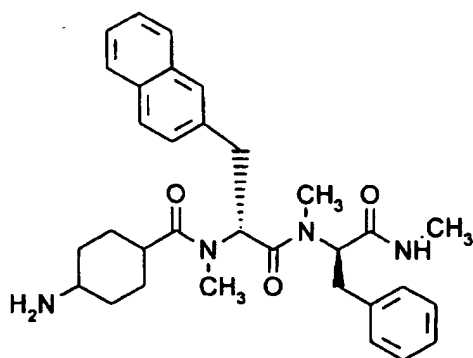


2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



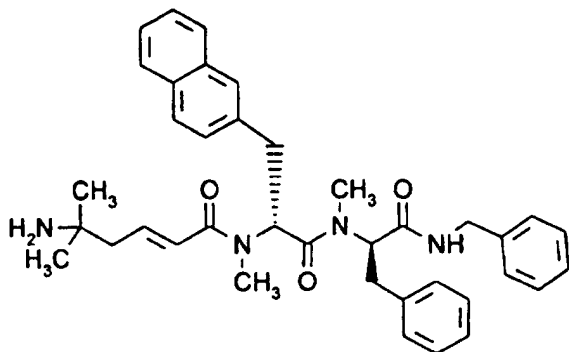
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4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

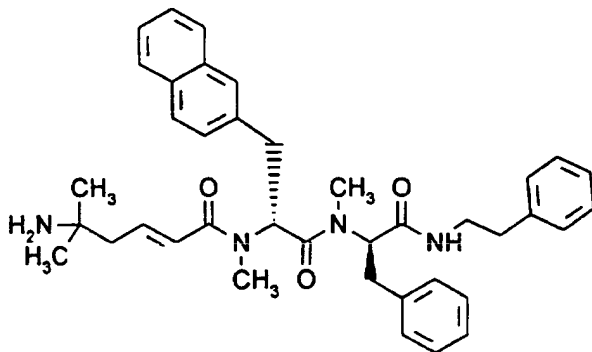


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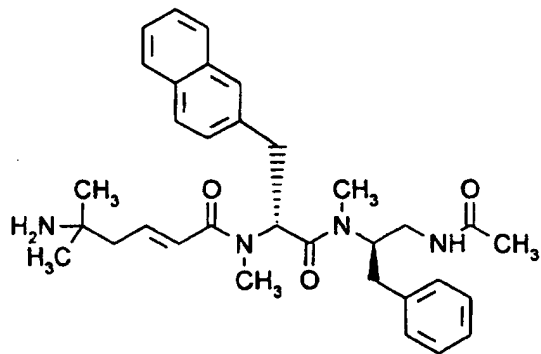
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(benzylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



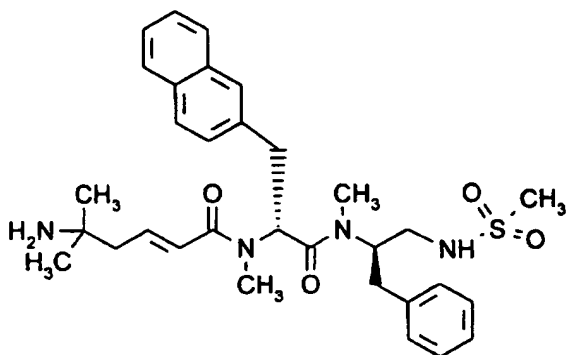
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(phenethylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



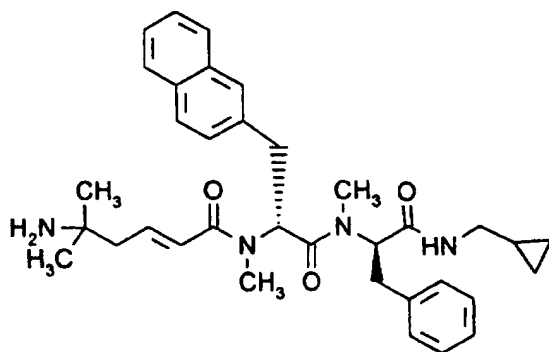
5 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(acetylaminomethyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



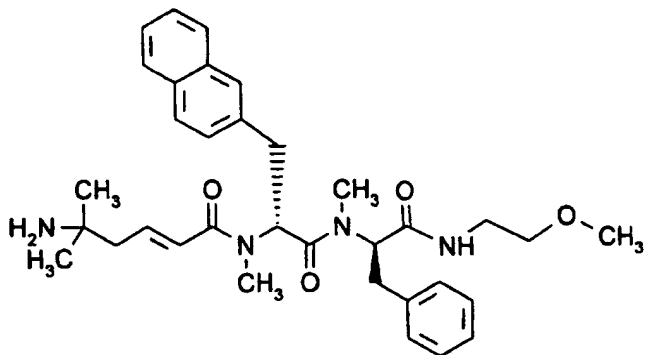
10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-1-(methylsulfonylaminomethyl)-2-phenylethyl]carbonyl}-2-(2-naphthyl)ethyl)amide:



(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-((cyclopropyl-
 5 methyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-
 methylamide:

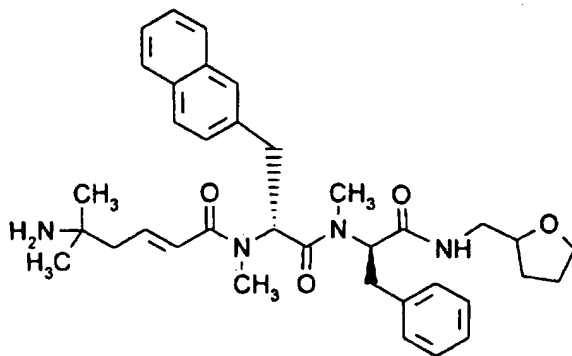


(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-(2-methoxy-
 10 ethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-
 methylamide:



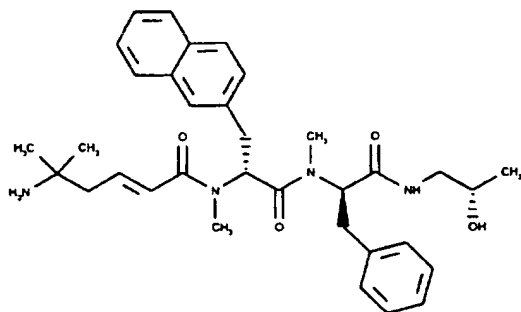
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-
 15 phenyl-1-((N-tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-
 naphthyl)ethyl)-N-methylamide:

naphthyl)ethyl)amide:



5

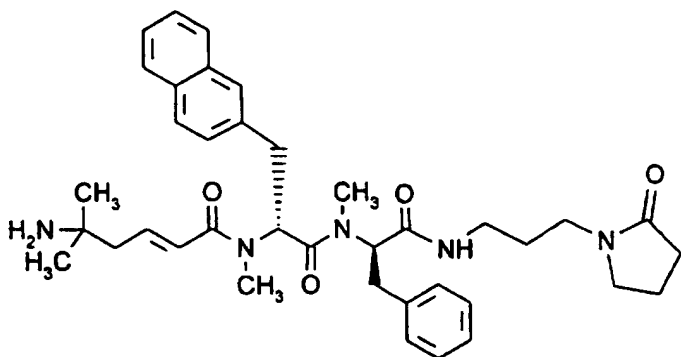
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-(2S)-2-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



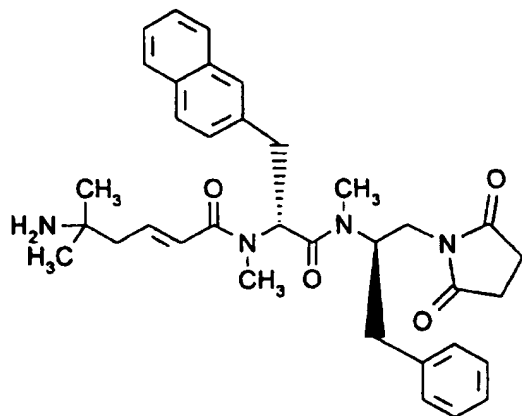
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(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(N-(3-(2-oxopyrrolidin-1-yl)propyl)carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

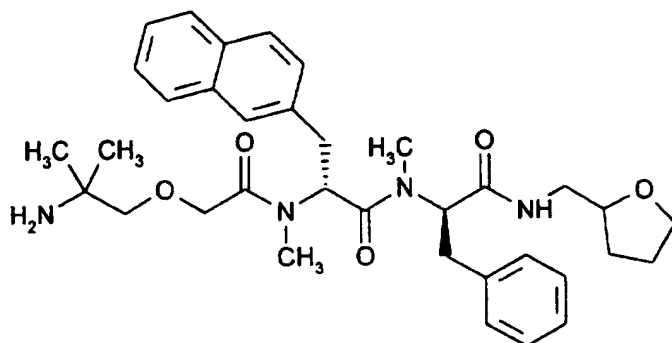
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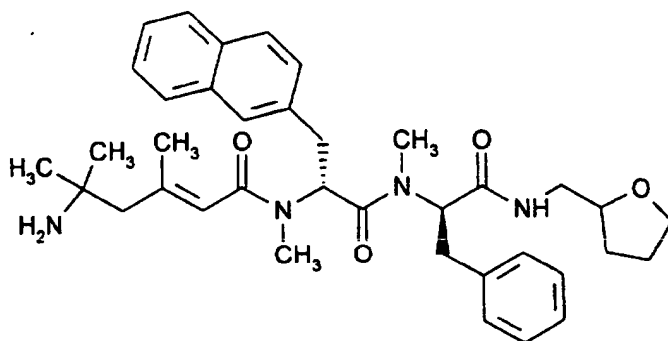
- (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-((2,5-dioxopyrrolidine-1-yl)methyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide:



- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide:

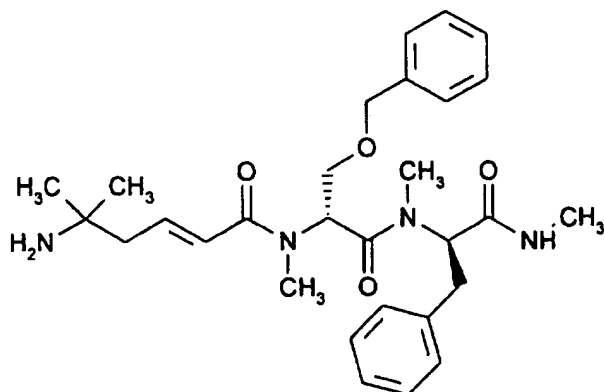


(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((2-tetra-hydrofuranyl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:

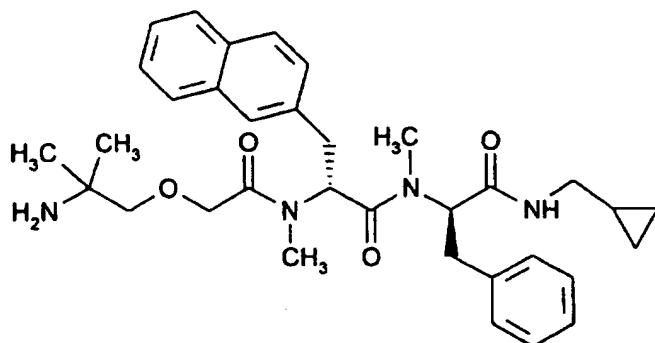


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(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylamide:

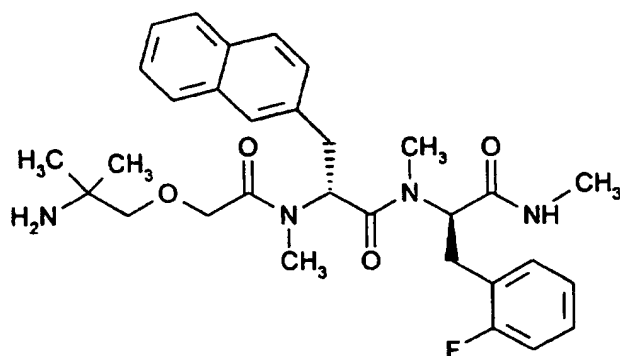


10 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-1-(cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)-propionamide:

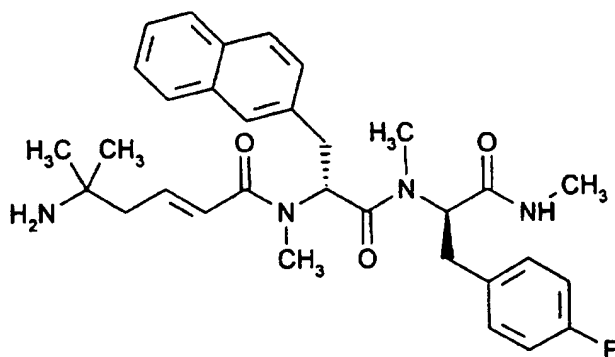


(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:

5

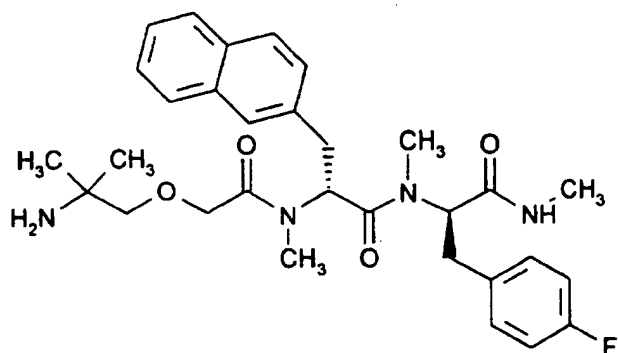


(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

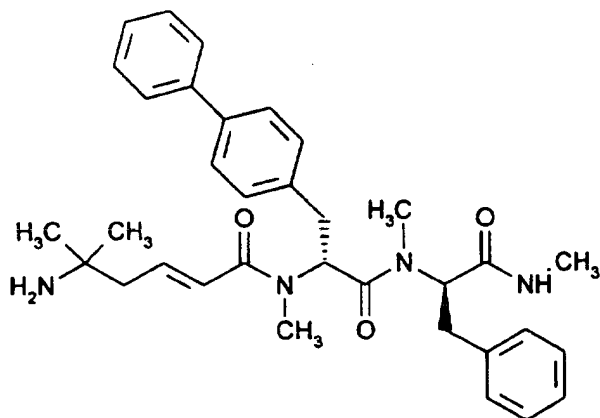


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(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)N-methylamino)-N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:

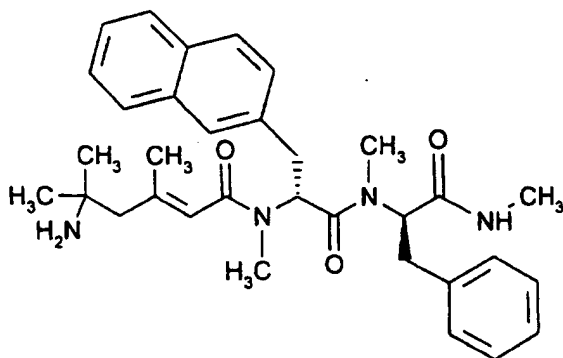


(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide:



5

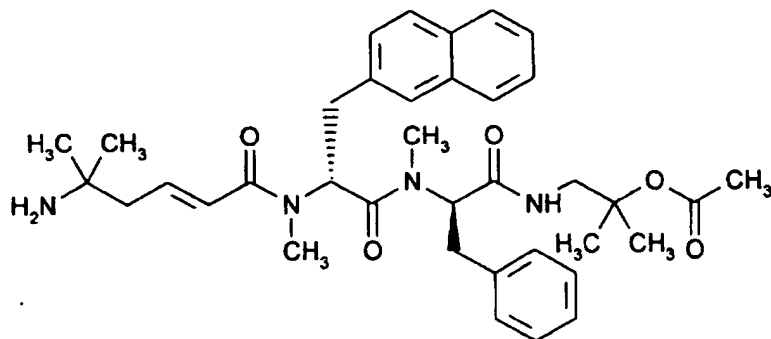
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



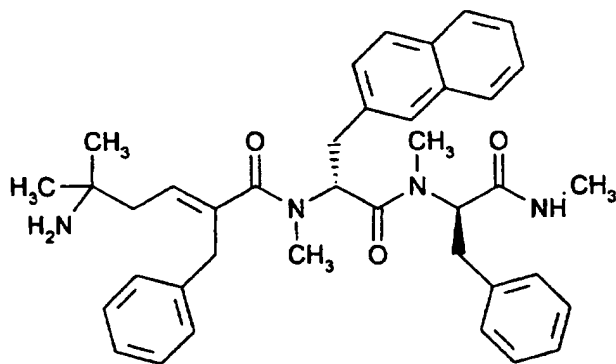
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2-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:

5

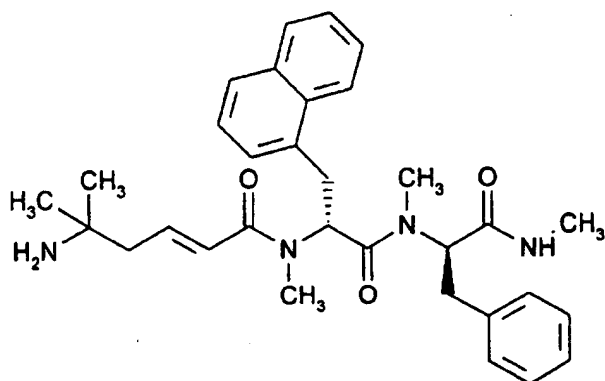


(2E)-5-Amino-2-benzyl-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



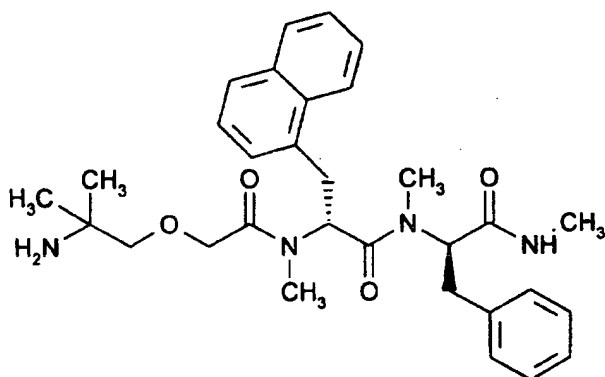
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(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(1-naphthyl)ethyl)amide:

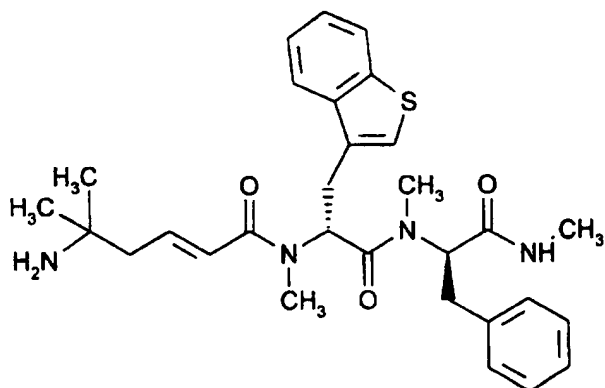


(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide:

5



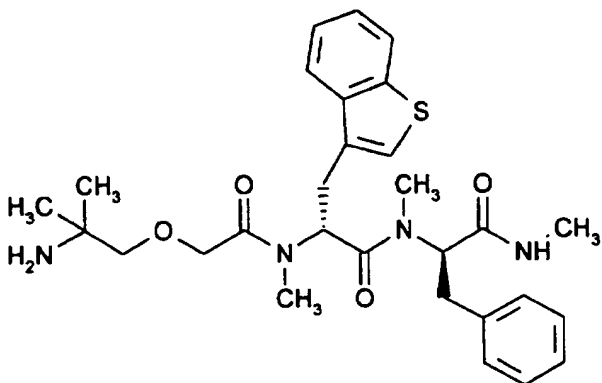
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-(benzo[b]thiophen-3-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)N-methylamide:



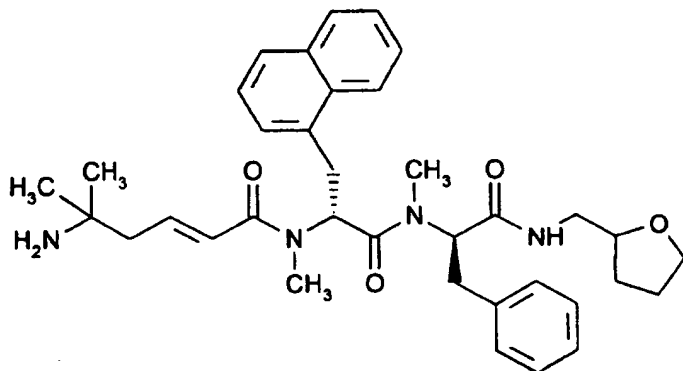
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(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-3-(benzo[b]thio-

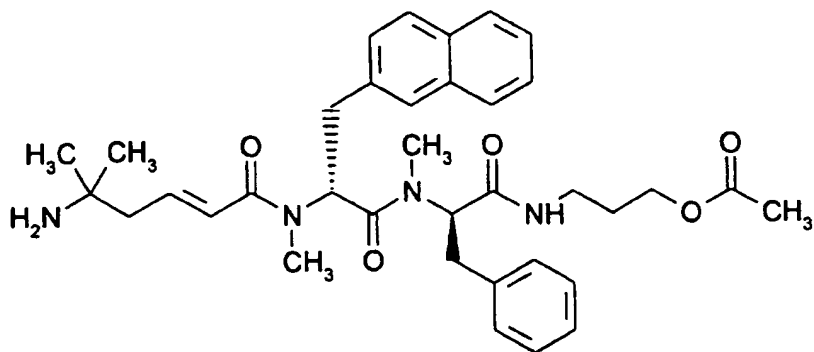
phen-3-yl)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)propionamide:



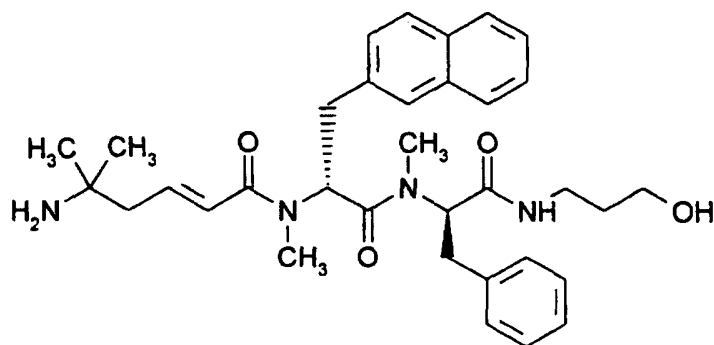
- 5 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide:



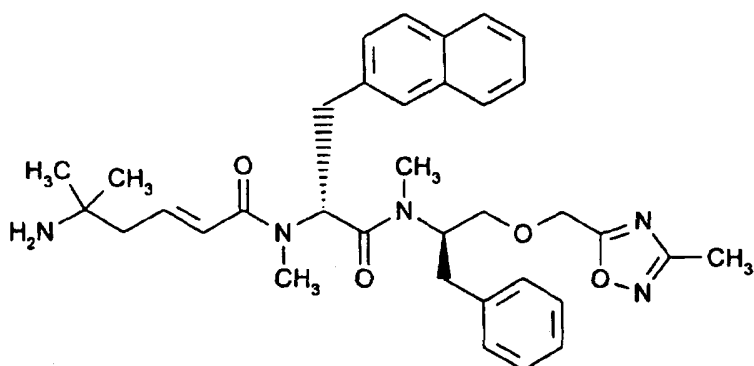
- 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-
10 naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



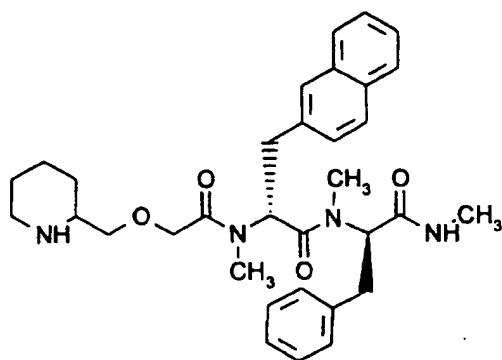
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



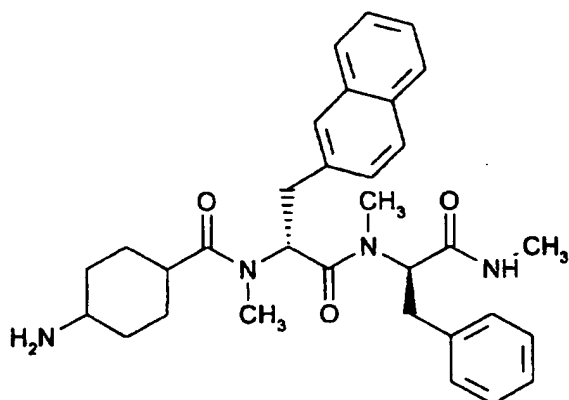
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



N-Methyl-N-((1R)-1-(methylcarbonyl)-2-phenylethyl)-2-(N-methyl-N-((2-piperidiny)methoxy)acetyl)amino)-3-(2-naphthyl)propionamide:

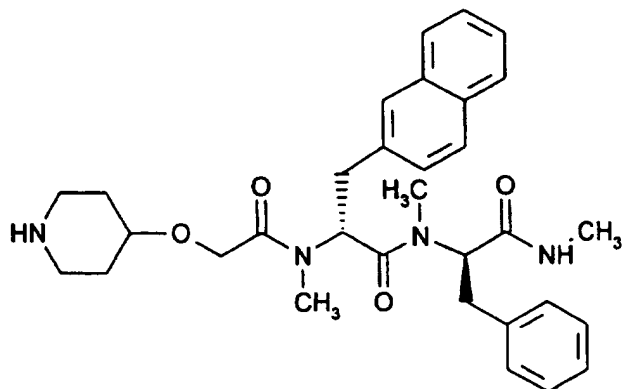


4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl]-2-(2-naphthyl)ethyl)amide:



5

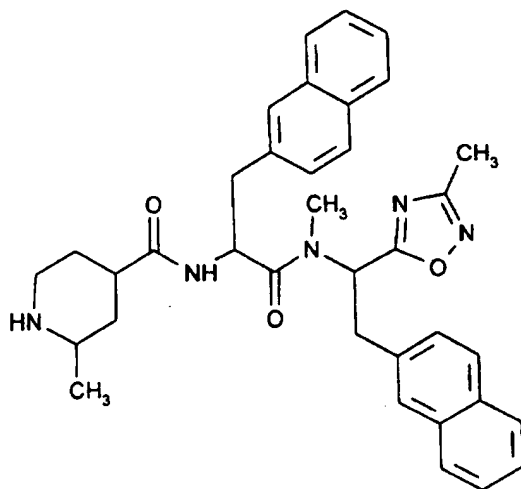
(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[[piperidin-4-yloxy]acetyl]amino)-3-(2-naphthyl)propionamide:



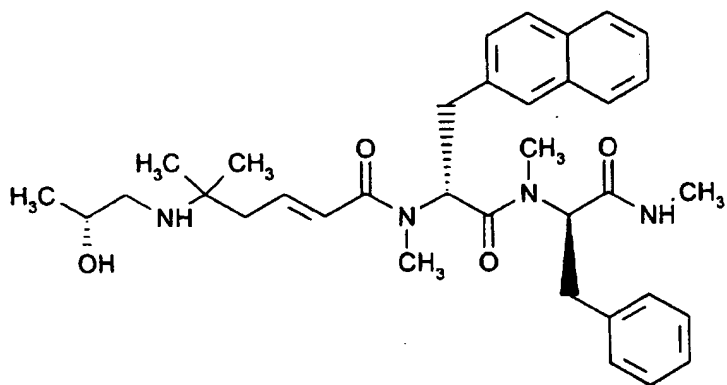
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2-Methyl-piperidine-4-carboxylic acid N-{1-[N-methyl-N-(1-(3-methyl-1,2,4-

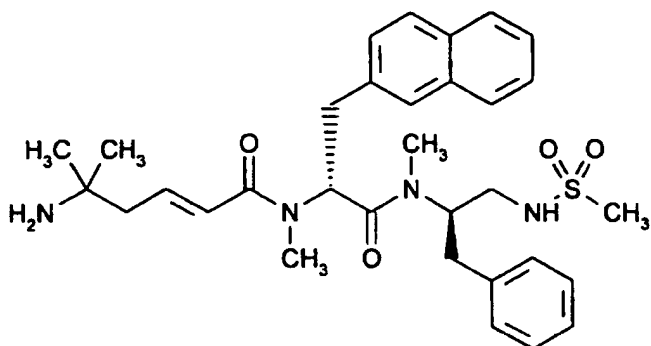
oxadiazol-5-yl)-2-(2-naphthyl)ethyl)carbamoyl]-2-(2-naphthyl)ethyl} amide:



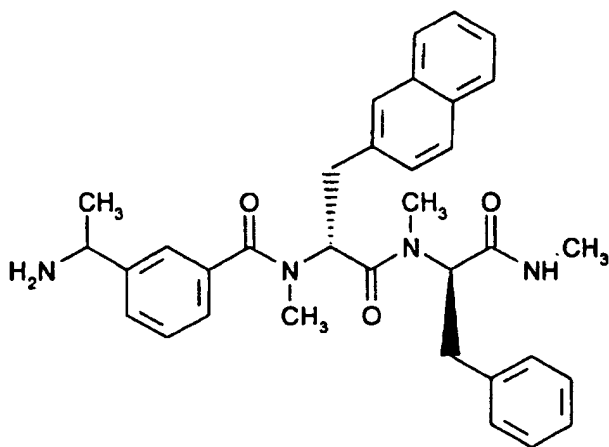
(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-Hydroxypropylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;



(2E)-5-Amino-N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-5-methyl-N-methylhex-2-enamide;



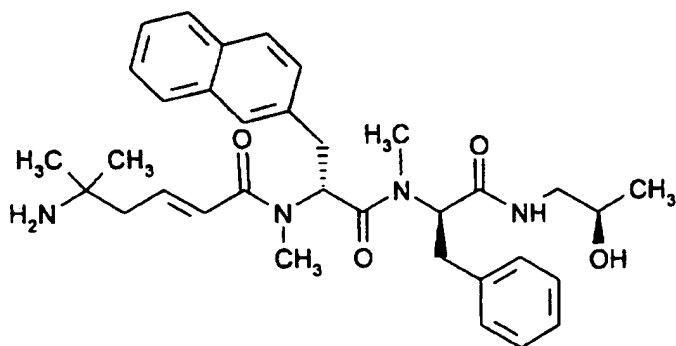
3-(1-Aminoethyl)benzoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



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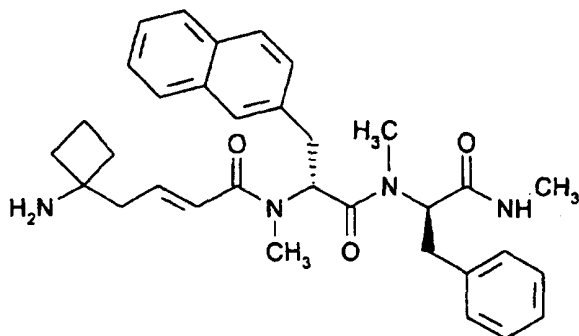
5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2R)-2-hydroxypropylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl) methylamide:

10



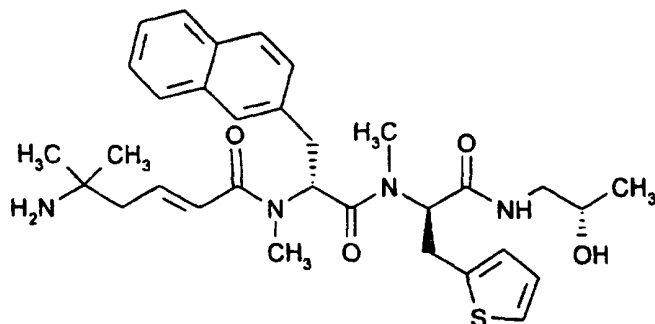
(4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-(((1R)-1-(1-methylcarbamoyl-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamid
e:

5



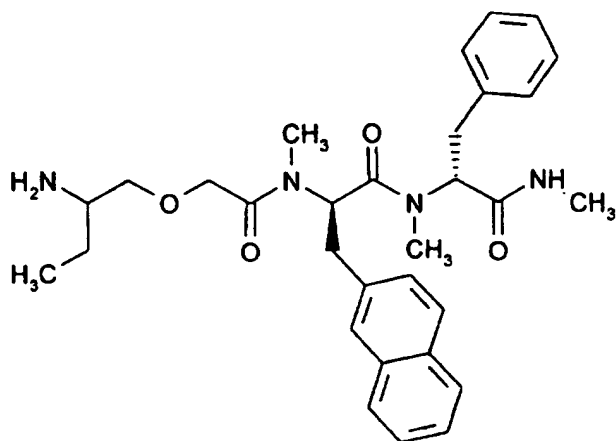
5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(2-thienyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.

10

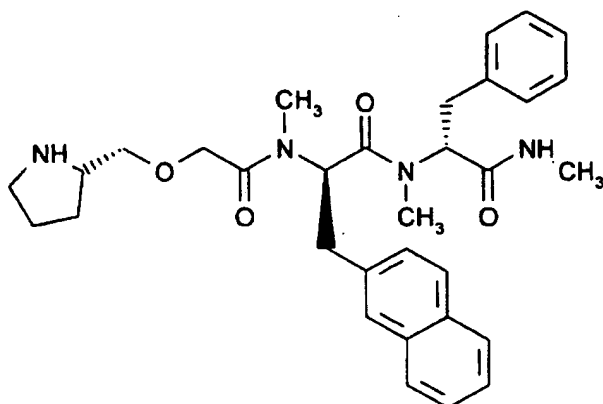


(2R)-2-(N-[(2R)-2-(N-[(2-Aminobutoxy)acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide:

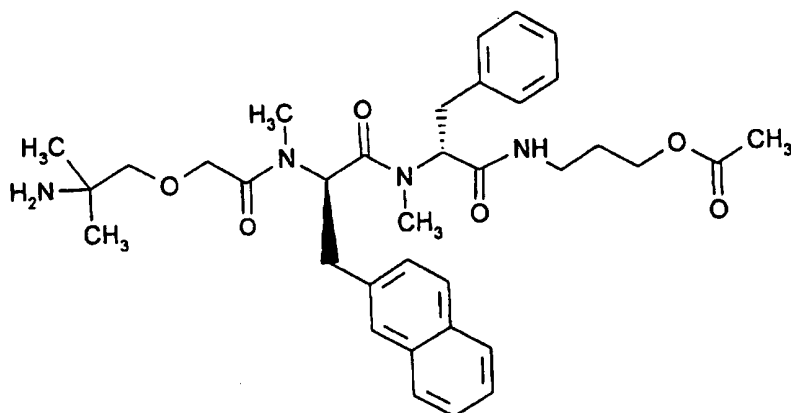
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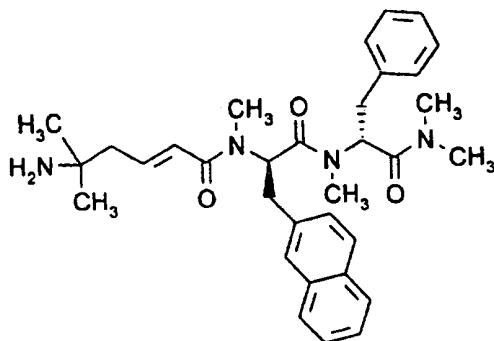
(2R)-N-Methyl-2-(N-methyl-N-((2R)-2-(N-methyl-N-(((2S)-pyrrolidin-2-yl)methoxy)acetyl)amino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionamide



3-((2R)-2-(N-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate

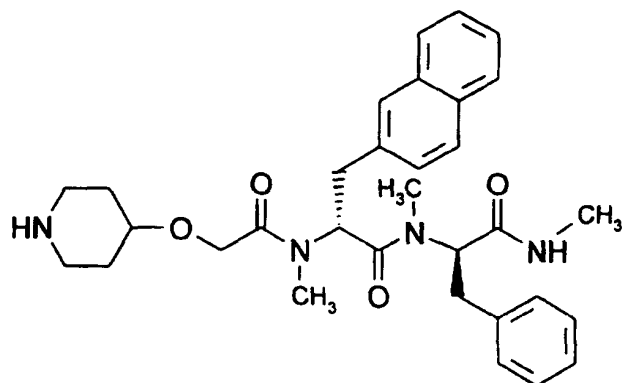


(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-
 5 (dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-
 2-(2-naphthyl)ethyl)-N-methylamide:



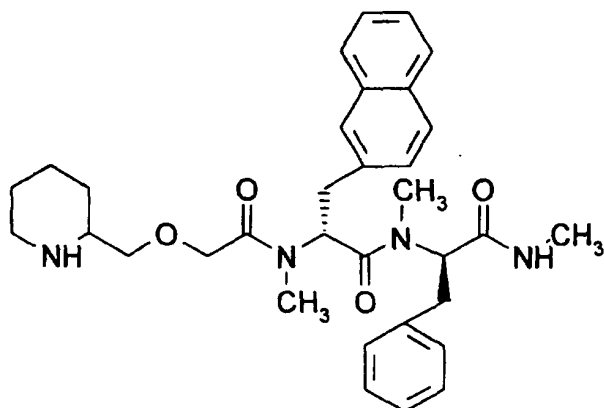
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(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-
 [{piperidin-4-yloxy}acetyl]amino)-3-(2-naphthyl) propionamide



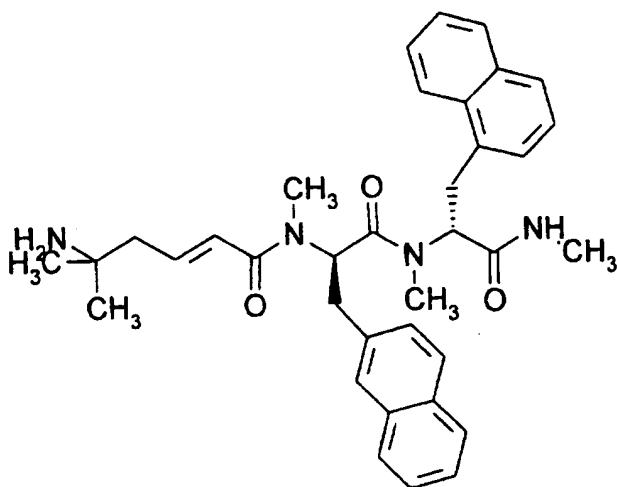
N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-((2-piperidiny)methoxy)acetyl)amino)-3-(2-naphthyl)propinamide

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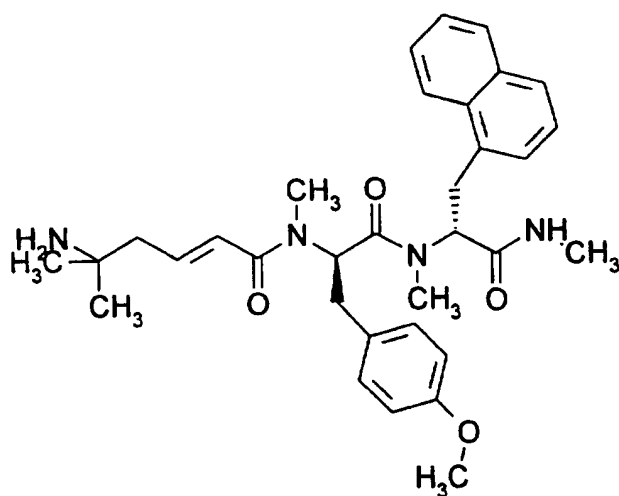


(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2-

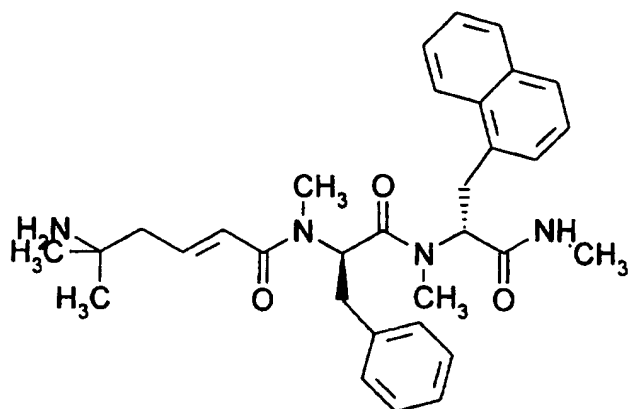
10 naphthyl)ethyl)amide:



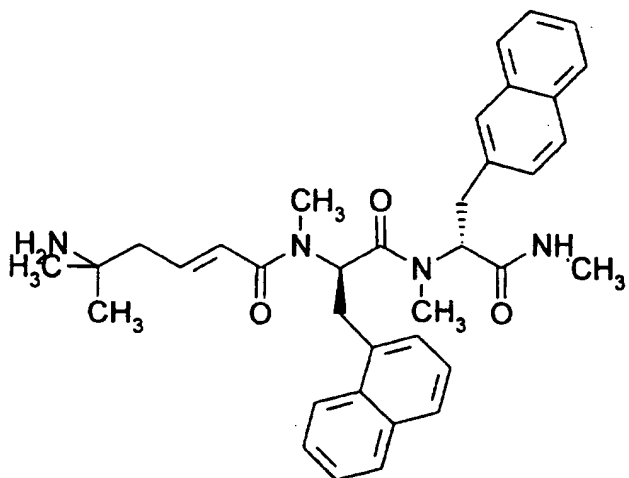
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



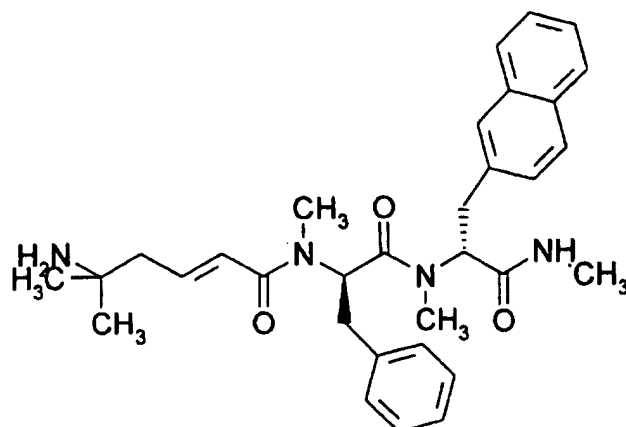
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



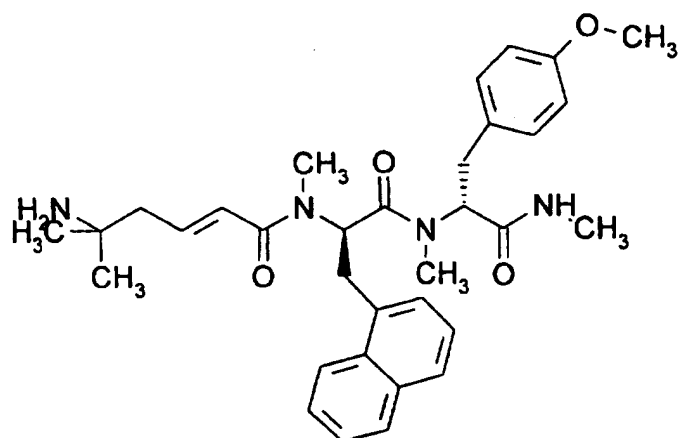
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



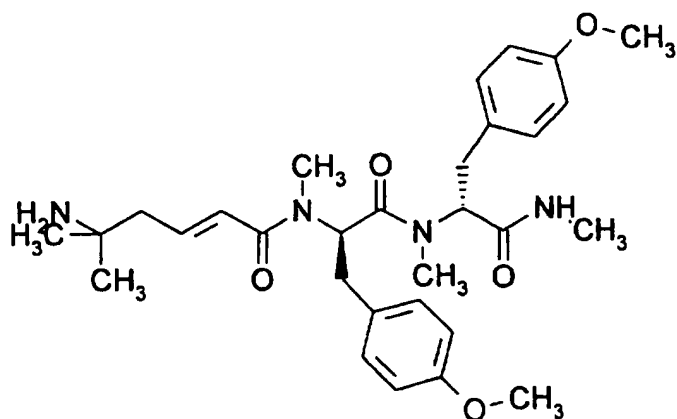
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



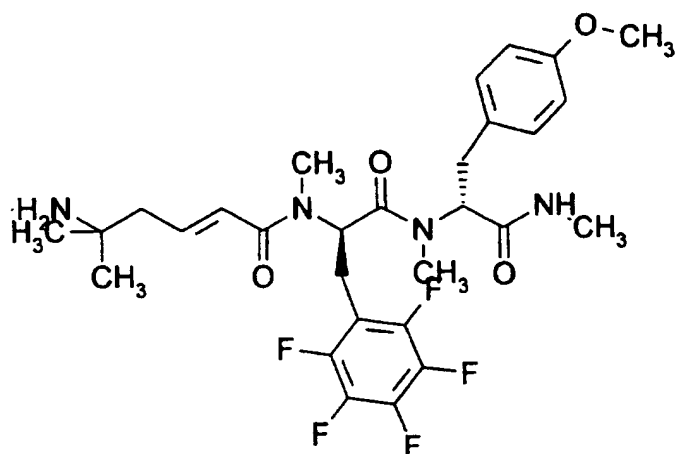
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



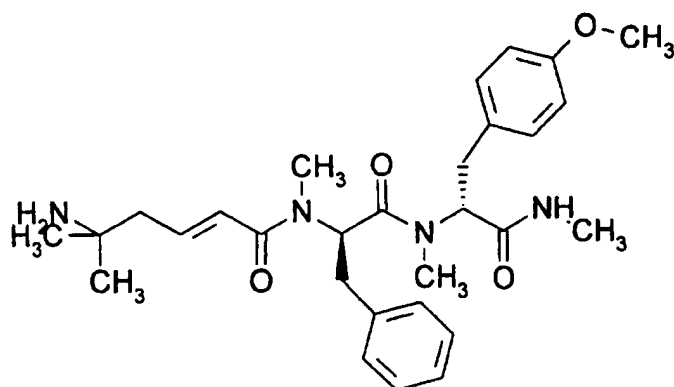
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



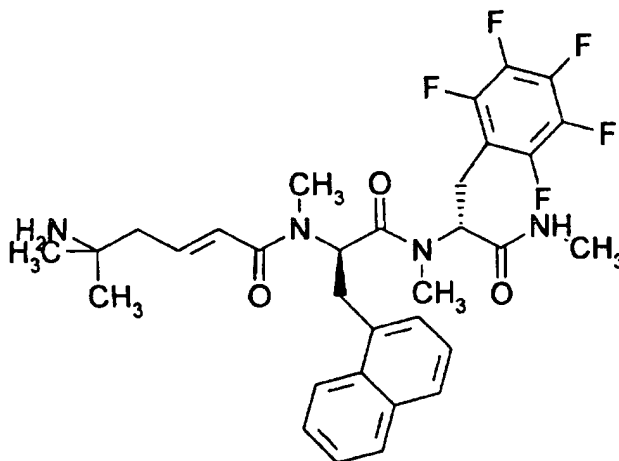
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-
 5 pentafluorophenyl)ethyl)amide:



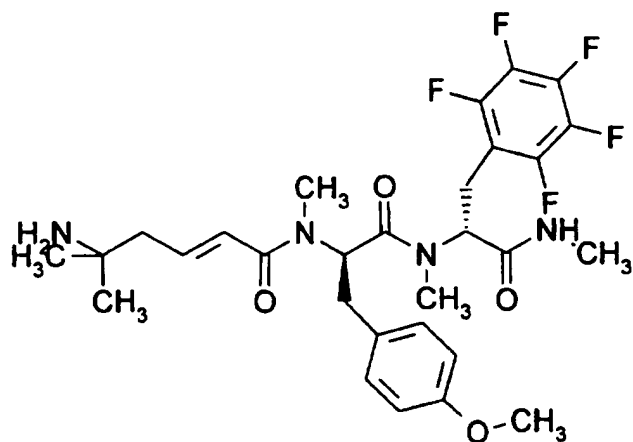
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-
 10 phenylethyl)amide:



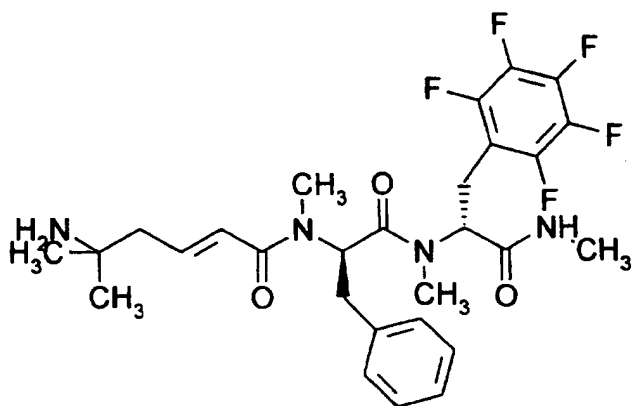
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



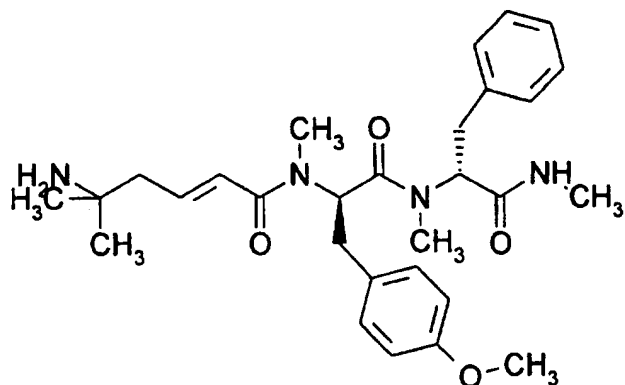
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



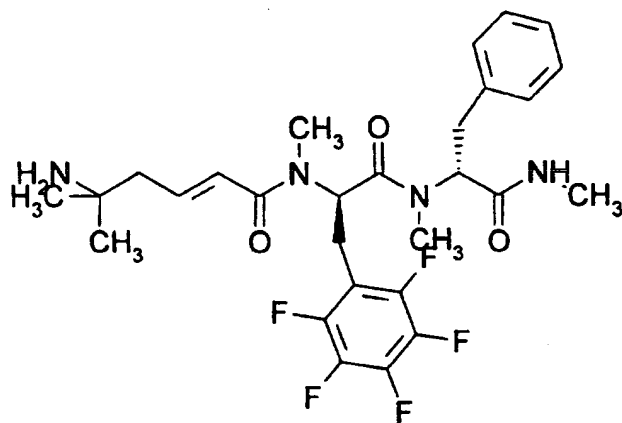
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-[(1R)-2-
 (2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-
 5 methylcarbamoyl)-2-phenylethyl)amide:



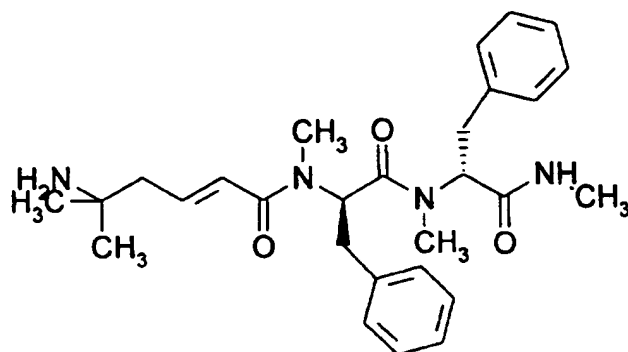
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-[(1R)-2-
 10 phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl)-2-(4-
 methoxyphenyl)ethyl)amide:



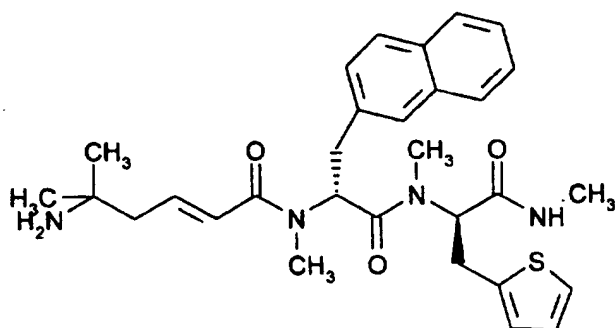
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-
 5 pentafluorophenyl)ethyl)amide:



(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:
 10



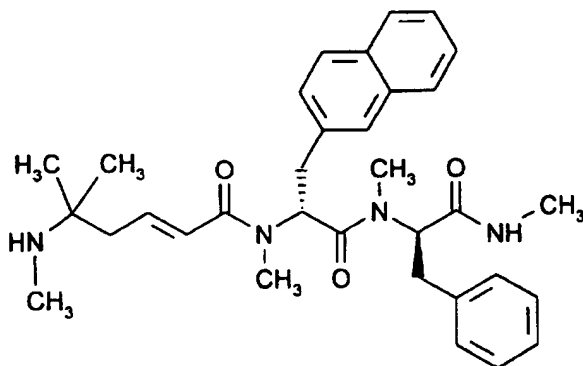
(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl) ethyl)carbamoyl)-2-
 5 (2-naphthyl)ethyl)amide



10

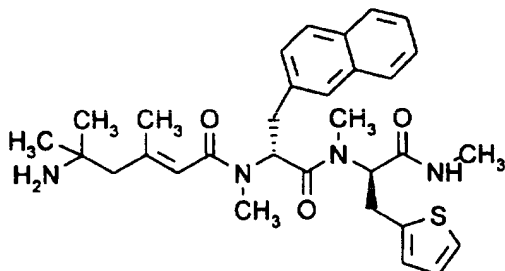
(2E)-5-Methyl-5-methylaminohex-2-enoic acid
 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenyl
 ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide

15



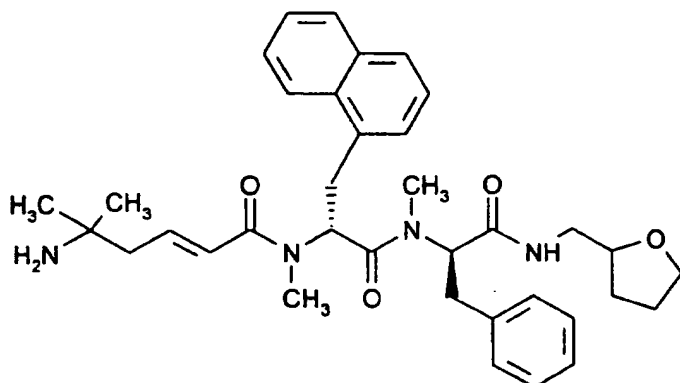
(2E)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl
 5)carbamoyl)-2-(2-naphthyl)ethyl) amide.



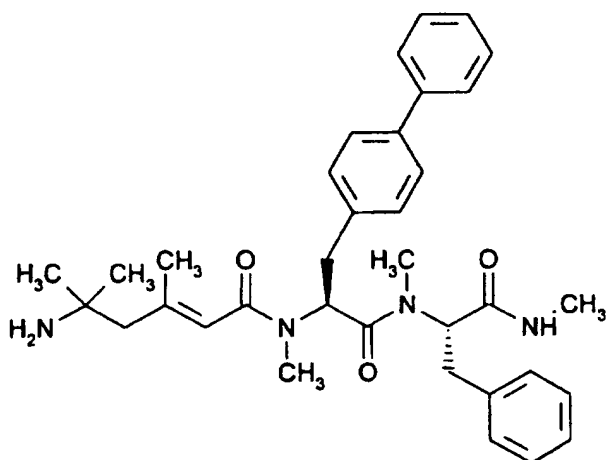
10 (2E)-5-Amino-5-methylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-(2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carba
 moyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide



5-Amino-3,5-dimethylhex-2-enoic acid

5 N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide.

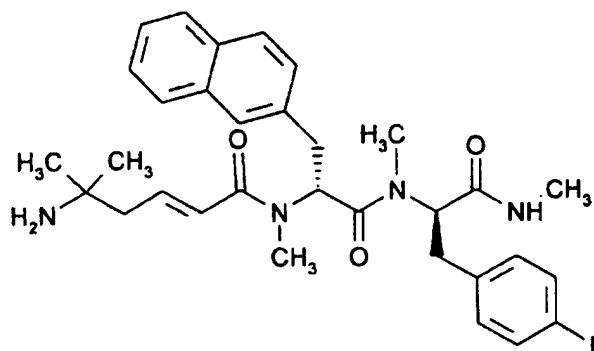


10

(2E)-5-Amino-5-methylhex-2-enoic acid

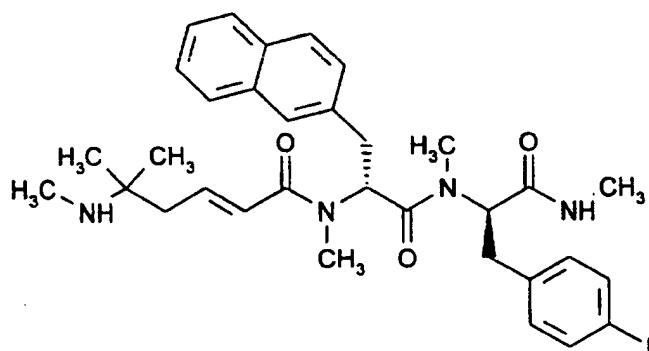
N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

15



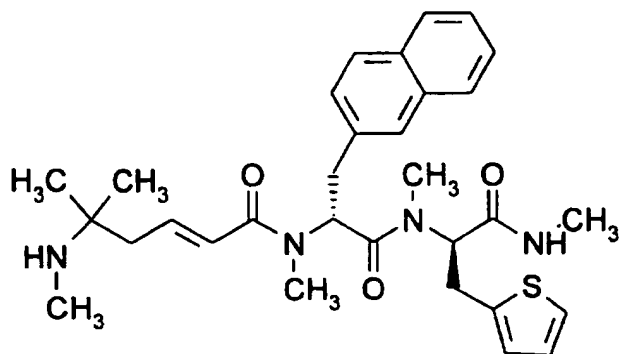
(2E)-5-Methyl-5-methylamino-2-hexenoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

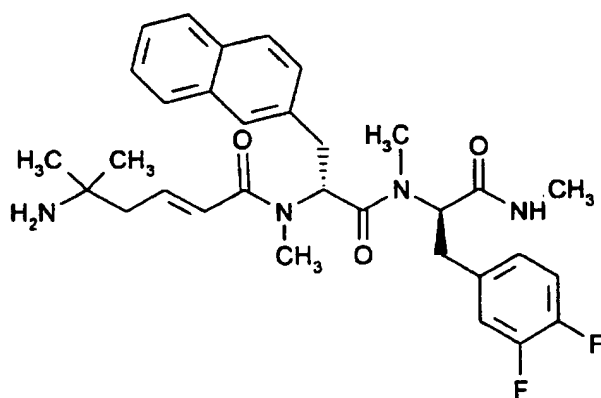


10 (2E) 5-Methyl-5-amino-5-methylhex-2-enoic

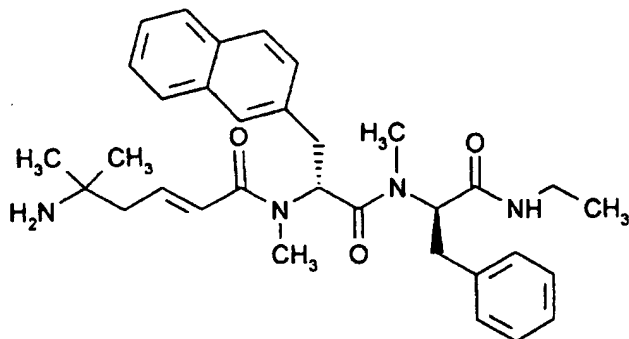
acid-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thien-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



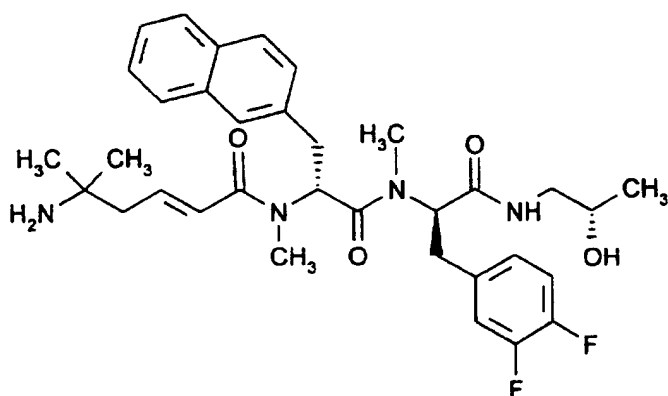
5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
2-(3,4-difluorophenyl)-1-methylcarbamoyl)ethyl)methylcar-
bamoyl)-2-(2-naphthyl)ethyl)methylamide



5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
2-phenyl-1-ethylcarbamoyl)ethyl)methylcar-
bamoyl)-2-(2-naphthyl)ethyl)methylamide



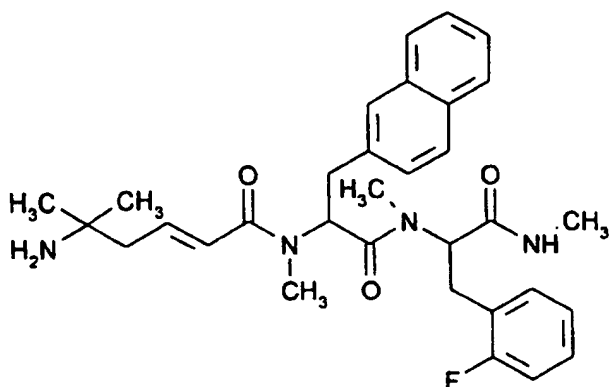
- 5 5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(3,4-difluorophenyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.



10

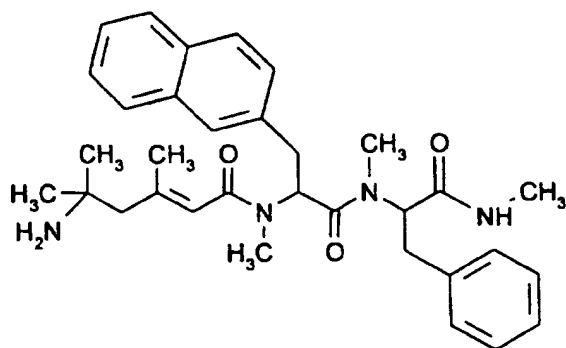
- 5-Amino-5-methyl-hex-2-enoic acid
(1-[[2-(2-fluorophenyl)-1-methylcarbamoyl]ethyl]methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.

15

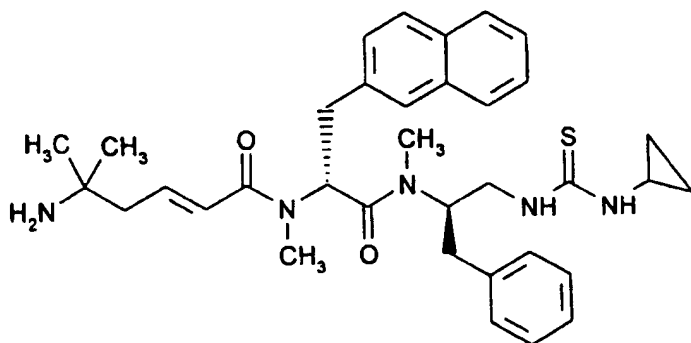


(2Z)-5-Amino-3,5-dimethylhex-2-enoic acid

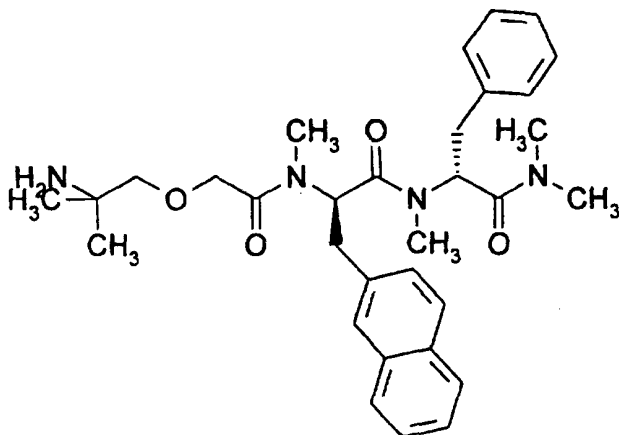
N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



(2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-3-(2-naphthyl)propionamide



(2R)-2-(N-[[2-Amino-2-methylpropoxy]acetyl]-N-methylamino)-N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide:



5

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide, and its acetate salt;

(2E)-5-Amino-5-methylhex-2-enoic acid

10 N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-2-(3,4-difluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

15 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

(2E) 4-(1-Aminocyclobutyl)-but-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide;

20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

- (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;
- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;
- 5 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;
- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;
- 10 3-(1-Aminomethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;
- (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-
- 15 yl)propionamide;
- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
- 20 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;
- 25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzyloxy)ethyl)benzamide;
- 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;
- 30 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;
- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;
- 5 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;
- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
- 10 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
- (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;
- 15 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;
- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;
- 20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;
- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;
- 25 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;
- (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;
- 30 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;
- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;
- 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;
- 10 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- 15 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;
- 20 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;
- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;
- 25 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
- 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
- 5 2-(2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;
- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;
- 10 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;
- (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;
- 15 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;
- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;
- 20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;
- (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- 25 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;
- 30 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;

- 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;
3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;
- 5 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;
(2R)-2-(N-(((2S)-2-Pyrrolidiny)l)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;
(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
- 10 ((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;
3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;
- 15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;
(2R)-2-(N-(((2S)-2-Pyrrolidiny)l)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;
- 20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;
3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;
- 25 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;
(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide;
(2R)-2-(N-(((2S)-2-Pyrrolidiny)l)methoxy)acetyl)-N-methylamino)-N-methyl-
- 30 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl) thyl)-3-(2-naphthyl)-propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-naphthyl)-ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

10 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-

15 yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

30 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 5 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;

10 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(biphen-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-

20 yl)propionamide; or

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide.

25 It is believed that compounds of formula I exhibit an improved resistance to proteolytic degradation by enzymes because they are non-natural, in particular because the natural amide bonds are replaced by non-natural amide bond mimetics. The increased resistance to proteolytic degradation combined with the reduced size of the compounds of the invention in comparison with known hormone
 30 releasing peptides is expected to improve their bioavailability compared to that of the peptides suggested in the prior literature.

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

- 5 The C₁₋₆-alkyl groups specified above are intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration, Examples of linear alkyl groups are methyl, ethyl, propyl, butyl, pentyl and hexyl. Examples of branched alkyl groups are isopropyl, sec-butyl, tert-butyl, isopentyl, and isohexyl. Examples of cyclic alkyl are cyclopropyl, cyclobutyl, cyclopentyl and
10 cyclohexyl.

Especially preferred C₁₋₆-alkyl groups are the C₁₋₃-alkyl groups. Preferred C₁₋₃-alkyl groups are methyl, ethyl, isopropyl and cyclopropyl.

- 15 The C₁₋₆-alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isoprpoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy,
20 cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

Especially preferred C₁₋₆-alkoxy groups are the C₁₋₃-alkoxy groups. Preferred C₁₋₃-alkoxy groups are methoxy, ethoxy, isopropoxy and cyclopropoxy.

- 25 In the present context, the term C₁₋₆-alkoxycarbonyl is intended to include the above defined C₁₋₆-alkoxy groups attached to a carbonyl moiety.

In the present context, the term C₁₋₆-alkoxycarbonyloxy is intended to include the above defined C₁₋₆-alkoxy groups attached to a carbonyloxy moiety.

30

In the present context, the term "aryl" is intended to include aromatic rings, such as carboxylic and heterocyclic aromatic rings selected from the group consisting of

phenyl, naphthyl, pyridyl, tetrazolyl, thiazolyl, imidazolyl, indolyl, quinoliny,
pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, thienyl, furanyl or oxadiazolyl
optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy. Aryl is
preferably phenyl, thienyl, imidazolyl, pyridyl, indolyl, oxadiazole or naphthyl
5 optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy.

The term "halogen" includes Cl, F, Br and I.

The compounds of the present invention may have one or more asymmetric
10 centres and it is intended that stereoisomers, as separated, pure or partially
purified stereoisomers or racemic mixtures thereof are included in the scope of the
invention.

Pharmaceutically acceptable acid addition salts of compounds of formula I include
15 those prepared by allowing the compound to react with an inorganic or organic acid
such as hydrochloric, hydrobromic, sulfuric, acetic, phosphoric, lactic, maleic,
phthalic, citric, glutaric, gluconic, methanesulfonic, salicylic, succinic, tartaric,
toluenesulfonic, trifluoroacetic, sulfamic or fumaric acid.

20 In another aspect, the present invention relates to a pharmaceutical composition
comprising, as an active ingredient, a compound of the general formula I or a
pharmaceutically acceptable salt thereof together with a pharmaceutically
acceptable carrier or diluent.

25 Pharmaceutical compositions containing a compound of the present invention may
be prepared by conventional techniques, e.g. as described in Remington's
Pharmaceutical Sciences, 1985. The compositions may appear in conventional
forms, for example capsules, tablets, aerosols, solutions, suspensions or topical
applications.

30

The pharmaceutical carrier or diluent employed may be a conventional solid or
liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose,

cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water.

- 5 Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier is used for oral administration, the preparation may be tableted,
10 placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

15

A typical tablet which may be prepared by conventional tableting techniques may contain:

20 Core:

Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg

25 Magnesium stearate

Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

30

*Acylated monoglyceride used as plasticizer for film coating.

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents,
5 e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising 50-200 mg of active ingredient together with a pharmaceutically
10 acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is suitably 0.1-500 mg/day, e.g. from about 5 to about 50 mg, such as about 10 mg per dose, when administered to patients, e.g. humans, as a drug.

15 The compounds of the invention possess interesting pharmacological properties, and it has been demonstrated that compounds of the general formula I possess the ability to release endogenous growth hormone *in vivo*. The compounds may therefore be used in the treatment of conditions which require increased plasma
20 growth hormone levels such as in growth hormone deficient humans or in elderly patients or livestock.

Thus, in a particular aspect, the present invention relates to a pharmaceutical composition for stimulating the release of growth hormone from the pituitary, the
25 composition comprising, as an active ingredient, a compound of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of stimulating the
30 release of growth hormone from the pituitary, the method comprising administering to a subject in need thereof an effective amount of a compound of the general formula I or a pharmaceutically acceptable salt thereof.

In a still further aspect, the present invention relates to the use of a compound of the general formula I or a pharmaceutically acceptable salt thereof for the preparation of a medicament for stimulating the release of growth hormone from the
5 pituitary.

To those skilled in the art, it is well known that the current and potential uses of growth hormone in humans are varied and multitudinous. Thus, compounds of formula I can be administered for purposes stimulating release of growth hormone
10 from the pituitary and would then have similar effects or uses as growth hormone itself. The uses of growth hormone may be summarized as follows: stimulation of growth hormone release in the elderly; prevention of catabolic side effects of glucocorticoids, prevention and treatment of osteoporosis, stimulation of the immune system, acceleration of wound healing, accelerating bone fracture repair,
15 treatment of growth retardation, treating renal failure or insufficiency resulting from growth retardation, treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome;
20 accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients, treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound
25 healing and psychosocial deprivation, treatment of pulmonary dysfunction and ventilator dependency, attenuation of protein catabolic responses after major surgery, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis, adjuvant treatment for ovulation induction; to stimulate thymic development and prevent the
30 age-related decline of thymic function, treatment of immunosuppressed patients, improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly, stimulation of osteoblasts, bone

remodelling and cartilage growth, stimulation of the immune system in companion animals and treatment of disorder of aging in companion animals, growth promoter in livestock and stimulation of wool growth in sheep.

- 5 For the above indications the dosage will vary depending on the compound of formula I employed, on the mode of administration and on the therapy desired. However, generally dosage levels between 0.0001 and 100 mg/kg body weight daily are administered to patients and animals to obtain effective release of endogenous growth hormone. Usually, dosage forms suitable for oral, nasal,
10 pulmonal or transdermal administration comprise from about 0.0001 mg to about 100 mg, preferably from about 0.001 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

- The compounds of formula I may be administered in pharmaceutically acceptable
15 acid addition salt form or, where appropriate, as a alkali metal or alkaline earth metal or lower alkylammonium salt. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

- Optionally, the pharmaceutical composition of the invention may comprise a
20 compound of formula I combined with one or more compounds exhibiting a different activity, e.g., an antibiotic or other pharmacologically active material.

- The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal,
25 pulmonary, transdermal or parenteral, the oral route being preferred.

Apart from the pharmaceutical use of the compounds of formula I, they may be useful in vitro tools for investigating the regulation of growth hormone release.

- 30 Compounds of formula I may also be useful in vivo tools for evaluating the growth hormone releasing capability of the pituitary. For example, serum samples taken before and after administration of these compounds to humans can be assayed for

growth hormone. Comparison of the growth hormone in each serum sample would directly determine the ability of the patients pituitary to release growth hormone.

Compounds of formula I may be administered to commercially important animals to
5 increase their rate and extent of growth, and to increase milk production.

A further use of growth hormone secretagogue compounds of formula I is in combination with other secretagogues such as GHRP (2 or 6), GHRH and its analogues, growth hormone and its analogues or somatomedins including IGF-1
10 and IGF-2.

Pharmacological Methods

Compounds of formula I may be evaluated in vitro for their efficacy and potency to
15 release growth hormone in rat pituitary primary cultures.

The isolation of rat pituitary cells is a modification of O. Sartor et al., Endocrinology 116, 1985, pp. 952-957. Male albino Sprague-Dawley rats (250 +/- 25 grams) were purchased from Møllegaard, Lille Skensved, Denmark. The rats were housed in
20 group cages (four animals/cage) and placed in rooms with 12 hour light cycle. The room temperature varied from 19-24°C and the humidity from 30 - 60%.

The rats were decapitated and the pituitaries dissected. The neurointermediate lobes were removed and the remaining tissue was immediately placed in icecold
25 isolation buffer (Gey's medium (Gibco 041-04030) supplemented with 0.25% D-glucose, 2% non-essential amino acids (Gibco 043-01140) and 1% bovine serum albumine (BSA) (Sigma A-4503)). The tissue was cut into small pieces and transferred to isolation buffer supplemented with 3.8 mg/ml of trypsin (Worthington #3707 TRL-3) and 330 mg/ml of DNase (Sigma D-4527). This mixture was
30 incubated at 70 rotations/min for 35 min at 37°C in a 95/5% atmosphere of O₂/CO₂. The tissue was then washed three times in the above buffer. Using a standard pasteur pipet, the tissue was then aspirated into single cells. After dispersion, cells

were filtered through a nylon filter (160 mm) to remove undigested tissue. The cell suspension was washed 3 times with isolation buffer supplemented with trypsin inhibitor (0.75 mg/ml, Worthington #2829) and finally resuspended in culture medium; DMEM (Gibco 041-01965) supplemented with 25 mM HEPES (Sigma H-3375), 4 mM glutamine (Gibco 043-05030H), 0.075% sodium bicarbonate (Sigma S-8875), 0.1% non-essential amino acid, 2.5% fetal calf serum (FCS, Gibco 011-06290), 3% horse serum (Gibco 034-06050), 10% fresh rat serum, 1 nM T₃ (Sigma T-2752) and 40 mg/L dexamethasone (Sigma D-4902) pH 7.3, to a density of 2×10^5 cells/ml. The cells were seeded into microtiter plates (Nunc, Denmark), 200 -
10 ml/well, and cultured for 3 days at 37°C and 8% CO₂.

Compound testing

After culturing, the cells were washed twice with stimulation buffer (Hanks Balanced
15 Salt Solution (Gibco 041-04020) supplemented with 1% BSA (Sigma A-4503), 0.25% D-glucose (Sigma G-5250) and 25 mM HEPES (Sigma H-3375) pH 7.3) and preincubated for 1 hour at 37°C. The buffer was exchanged with 90 ml stimulation buffer (37°C). Ten ml test compound solution was added and the plates were incubated for 15 min at 37°C and 5% CO₂. The medium was decanted and
20 analyzed for GH content in an rGH SPA test system.

All compounds were tested in doses ranging from 10 pM to 100 mM. A dose-response relation was constructed using the Hill equation (Fig P, Biosoft). The efficacy (maximal GH released, E_{max}) was expressed in % of the E_{max} of GHRP-6.
25 The potency (EC₅₀) was determined as the concentration inducing half maximal stimulation of the GH release.

30 Compounds of formula I may be evaluated for their metabolic stability.

Compounds were dissolved at a concentration of 1 mg/ml in water. 25 ml of this solution is added to 175 ml of the respective enzyme-solution (resulting in an enzyme:substrate ratio (w/w) of approximately 1:5). The solution is left at 37°C overnight. 10 ml of the various degradation solutions is analyzed against a
5 corresponding zero-sample using flow injection electrospray mass spectrometry (ESMS) with selected ion monitoring of the molecular ion. If the signal has decreased more than 20% compared to the zero-sample, the remainder of the solution is analyzed by HPLC and mass spectrometry in order to identify the extent and site(s) of degradation precisely.

10

Several standard peptides (ACTH 4-10, Angiotensin 1-14 and Glucagon) have been included in the stability tests in order to verify the ability of the various solutions to degrade peptides.

15 Standard peptides (angiotensin 1-14, ACTH 4-10 and glucagon) were purchased from Sigma, MO, USA)

Enzymes (trypsin, chymotrypsin, elastase aminopeptidase M and carboxypeptidase Y and B) were all purchased from Boehringer Mannheim GmbH (Mannheim,

20 Germany)

Pancreatic enzyme mix: trypsin, chymotrypsin and elastase in 100 mM ammoniumbicarbonate pH 8.0 (all concentrations 0.025 mg/ml).

25 Carboxypeptidase mix: carboxypeptidase Y and B in 50 mM ammoniumacetate pH 4.5 (all concentrations 0.025 mg/ml).

Aminopeptidase M solution: aminopeptidase M (0.025 mg/ml) in 100 mM ammoniumbicarbonate pH 8.0

30

Mass spectrometric analysis was performed using two different mass spectrometers. A Sciex API III triple quadrupole LC-MS instrument (Sciex

instruments, Thornhill, Ontario) equipped with an electrospray ion-source and a Bio-Ion 20 time-of-flight Plasma Desorption instrument (Bio-Ion Nordic AB, Uppsala, Sweden).

- 5 Quantification of the compounds (before and after degradation) was done on the API III instrument using single ion monitoring of the molecular ion in question with flow injection of the analyte. The liquid flow (MeOH:water 1:1) of 100 ml/min was controlled by an ABI 140B HPLC unit (Perkin-Elmer Applied Biosystems Divisions, Foster City, CA). The instrument parameters were set to standard operation
- 10 conditions, and SIM monitoring was performed using the most intense molecular ion (in most cases this corresponded to the doubly charged molecular ion).

- Identification of degradation products furthermore involved the use of plasma desorption mass spectrometry (PDMS) with sample application on nitrocellulose
- 15 coated targets and standard instrumental settings. The accuracy of the hereby determined masses is generally better than 0.1%.

- Separation and isolation of degradation products was done using a HY-TACH C-18 reverse phase 4.6x105 mm HPLC column (Hewlett-Packard Company, Palo Alto,
- 20 CA) with a standard acetonitril: TFA separation gradient. The HPLC system used was HP1090M (Hewlett-Packard Company, Palo Alto, CA).

Peptide derivative	MW/SIM ion (amu)	Carboxy-peptidase mix	Pan. enzyme mix
Standards			
ACTH 4-10	1124.5/562.8	+	-
Glucagon	3483/871.8	-	-
Insulin (B23-29)	859.1/430.6		
Angiotensin 1-14	1760.1/881.0	-	-
GHRP-2	817.4/409.6	-	-
GHRP-6	872.6/437.4	-	-

+: Stable (less than 20% decrease in SIM signal after 24 h in degradation solution)

5 -: Unstable (more than 20% decrease in SIM signal after 24 h in degradation solution)

Any novel feature or combination of features described herein is considered essential to this invention.

EXAMPLES:

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be
5 construed as limiting.

The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts (d) are given in parts per million (ppm) and only selected peaks are given. mp is
10 melting point and is given in °C. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

15

Abbreviations:

TLC:	thin layer chromatography
DMSO:	dimethylsulfoxide
CDCl ₃ :	deuterated chloroform
20 DMF:	N,N-dimethylformamide
min:	minutes
h:	hours

HPLC-Analysis:

25

Method B1.

The RP-HPLC analysis was performed using UV detection at 214nm and a Vydac 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1ml/minute. Two solvent systems were used:
30 Solvent system I: 0.1% Trifluoroacetic acid in acetonitrile. Solvent system II: 0.1% Trifluoroacetic acid in water.

The column was equilibrated with a mixture composed of 5% of solvent system I and 95% of solvent system II. After injection of the sample a gradient of 5% to 60% of solvent system I in solvent system II was run over 50 minutes. The gradient was then extended to 100% of solvent system I over 15 minutes followed
5 by isocratic elution with 100% of this system for 5 minutes.

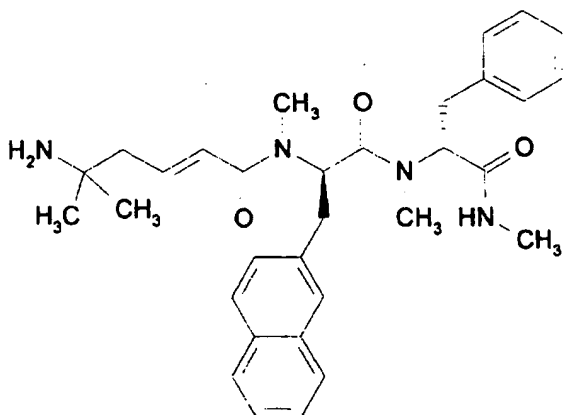
Method A1.

The RP-analysis was performed using UV detections at 214, 254, 276, and 301 nm on a Vydac 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The
10 Separations Group, Hesperia), which was eluted at 1 mL/min at 42°C. The column was equilibrated with 5% acetonitrile in a buffer consisting of 0.1 M ammonium sulfate, which was adjusted to pH 2.5 with 4M sulfuric acid. after injection the sample was eluted by a gradient of 5% to 60% acetonitrile in the same buffer during 50 min.

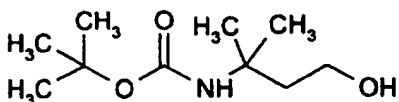
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Example 1:

(2E) 5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide
20 hydrochloride:



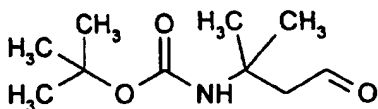
3-Hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester:



Step A: At 0 °C, ethyl chloroformate (1.10 mL, 11.5 mmol) was given dropwise to a solution of 3-tert-butoxycarbonylamino-3-methylbutanoic acid (2.50 g, 11.5 mmol) and triethylamine (1.92 mL, 13.8 mmol) in tetrahydrofuran (10 mL). The solution was stirred for 40 min at 0 °C. The formed precipitate was filtered off and washed with tetrahydrofuran (20 mL). The liquid was immediately cooled to 0 °C. A 2M solution of lithium boronhydride in tetrahydrofuran (14.4 mL, 28.8 mmol) was added dropwise. The solution was stirred at 0 °C for 2 h, and then warmed to room temperature over a period of 4 h. It was cooled to 0 °C. Methanol (5 mL) was added carefully. 1N Hydrochloric acid (100 mL) was added. The solution was extracted with ethyl acetate (2 x 100 mL, 3 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was chromatographed on silica (110 g) with ethyl acetate/heptane 1:2 to give 1.84 g of 3-hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): δ 1.33 (s, 6 H); 1.44 (s, 9 H); 1.88 (t, 2 H); 1.94 (br, 1 H); 3.75 (q, 2 H); 4.98 (br, 1 H).

3-(tert-Butoxycarbonylamino)-3-methylbutanal:



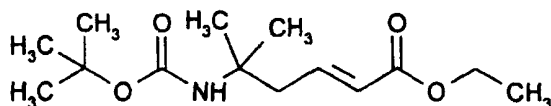
Step B: DMSO (1.22 mL, 17.2 mmol) was added to a solution of oxalyl chloride (1.1 mL, 12.9 mmol) at -78 °C in dichloromethane (15 mL). The mixture was stirred for 15 min at -78 °C. A solution of 3-hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester (1.75 g, 8.6 mmol) in dichloromethane (10 mL) was added dropwise over a

period of 15 min. The solution was stirred at -78 °C for another 15 min.

Triethylamine (6.0 mL, 43 mmol) was added. The solution was stirred at -78 °C for 5 min and then warmed to room temperature. The solution was diluted with dichloromethane (100 mL) and extracted with 1N hydrochloric acid (100 mL). The aqueous phase was extracted with dichloromethane (50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica (140 g) with ethyl acetate/heptane (1:3) to give 1.10 g of 3-(tert-butoxycarbonylamino)-3-methylbutanal.

¹H-NMR (CDCl₃): δ 1.39 (s, 6 H); 1.45 (s, 9 H); 2.85 (d, 2 H); 4.73 (br. 1 H); 9.80 (t, 1 H).

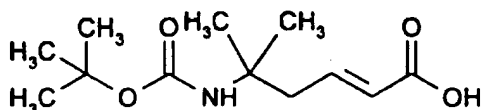
Ethyl (2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoate:



Step C: Triethylphosphonoacetate (1.96 mL, 9.8 mmol) was dissolved in tetrahydrofuran (30 mL). Potassium tert-butoxide (1.10 g, 9.8 mmol) was added. The solution was stirred for 40 min at room temperature. A solution of 3-(tert-butoxycarbonylamino)-3-methylbutanal (1.10 g, 5.5 mmol) in Tetrahydrofuran (6 mL) was added. The solution was stirred at room temperature. for 75 min. It was diluted with ethyl acetate (100 mL) and 1N hydrochloric acid (100 mL). The phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution (60 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica (90 g) with ethyl acetate/heptane (1:4) to give 1.27 g of ethyl (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoate.

¹H-NMR (CDCl₃): d 1.30 (s, 6 H); 1.30 (t, 3 H); 1.46 (s, 9 H); 2.62 (d, 2 H); 4.27 (q, 2 H); 4.42 (br, 1 H); 5.88 (d, 1 H); 6.94 (td, 1 H).

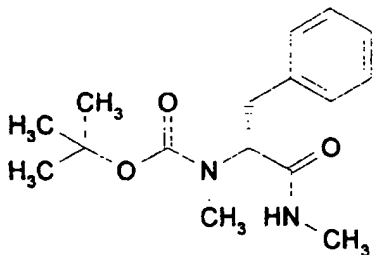
5 (2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid:



Step D: Ethyl (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoate (1.233 g,
 10 4.54 mmol) was dissolved in dioxane (20 mL). Lithium hydroxide (0.120 g, 5.00 mmol) was added as a solid. Water (10 mL) was added, until a clear solution was reached. The solution was stirred 16 h at room temperature. The solution was diluted with water (70 mL) and was extracted with tert-butyl methyl ether (2 x 100 mL). The aqueous phase was acidified with 1N sodium hydrogensulfate solution
 15 (pH = 1) and was extracted with tert-butylmethylether (3 x 70 mL). The organic phases were combined and dried over magnesium sulfate. The solvent was removed in vacuo to give 1.05 g of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid. The crude product was used for further syntheses.

¹H-NMR (DMSO d₆): d 1.15 (s, 6 H); 1.35 (s, 9 H); 2.53 (d, 2 H); 5.75 (d, 1 H); 6.57
 20 (br, 1 H); 6.75 (td, 1 H); 12.15 (s, 1 H).

N-Methyl-N-((R)-1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester:

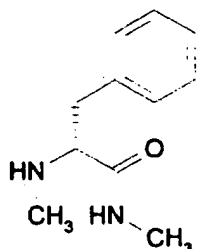


25 Step E: N-Tert-butoxycarbonyl-N-methyl-D-phenylalanine (1.22 g, 4.4 mmol), 1-hydroxybenzotriazole hydrate(0.59 g, 4.4 mmol) and 1-ethyl-3-(3-dimethyl-

aminopropyl)carbodiimid hydrochloride (0.88 g, 4.6 mmol) were dissolved in N,N-dimethylformamide (25 mL) and stirred for 30 min. Methylamine (0.51 g of a 40% solution in methanol, 6.6 mmol) was added and the mixture was stirred overnight. Methylene chloride (80 mL) and water (100 mL) were added and the phases were
5 separated. The organic phase was washed with sodium hydroxide (20 mL, 1N), sodium hydrogensulfate (50 mL, 10 %) and water (50 mL). The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to afford 1.39 g of N-methyl-N-((R)1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester.

10 ¹H-NMR (CDCl₃): d 1.25, 1.35 (two s (br), 9H); 2.73-2.94 (m, 7H); 3.30-3.50 (m, 1H); 4.68, 4.90 (two m, 1H); 5.90, 6.12 (two s (br); 1H); 7.12-7.25 (m, 5H).

(R)-N-Methyl-2-methylamino-3-phenylpropionamide:

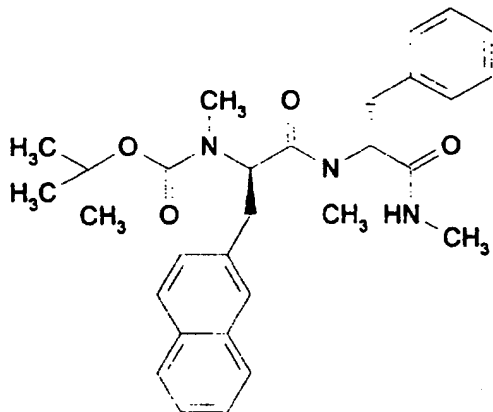


15

Step F: N-Methyl-N-((R)1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester (1.39 g, 7.23mmol) was dissolved in a mixture of trifluoroacetic acid (5 mL) and methylene chloride (10 mL) and stirred for 45 min. The volatiles were removed in vacuo and the residue was stirred with a mixture of ethyl acetate (100 mL) and
20 water (100 mL). Sodium hydrogen carbonate (50 mL, saturated) was added and the phases were separated. The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to afford 330 mg of (R)-N-methyl-2-methylamino-3-phenylpropionamide.

25 ¹H-NMR (CDCl₃): d 2.1 (s(br), 3H); 2.32 (s, 3H); 2.77 (dd, 1H); 2.81 (two s, 3H); 3.21 (dd, 1H); 3.32 (dd, 1H); 7.12 (s(br), 1H); 7.20-7.34 (m, 5H).

N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester:



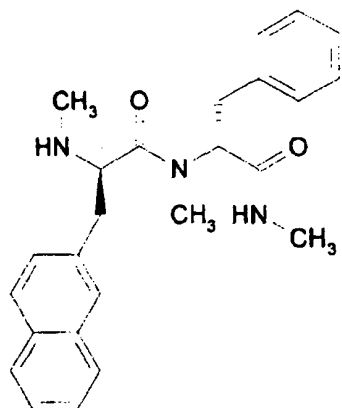
- 5 **Step G:** (R)-Tert-butoxycarbonyl-N-methylamino-3-(2-naphthyl)propionic acid (548 mg, 1.66 mmol) was dissolved in methylene chloride (5 mL); 1-hydroxy-7-azabenzotriazole (227 mg, 1.66 mmol) was added along with N,N-dimethylformamide (2 mL). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (351 mg, 1.83 mmol) was added and the solution was stirred for 15
- 10 min. (R)-N-Methyl-2-methylamino-3-phenylpropionamide (320 mg, 1.66 mmol) dissolved in methylene chloride (4 mL) and diisopropylethylamine (0.28 mL, 1.66 mmol) were added and the mixture was stirred overnight. Methylene chloride (50 mL) was added and the organic phase was washed with water (100 mL), sodium hydrogensulfate (50 mL, 5%) and sodium hydrogen carbonate (50 mL, saturated).
- 15 The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo. The residue was chromatographed (silica, 2 x 45 cm) using ethylacetate/methylene chloride (1:1) to afford 604 mg of N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)-ethyl)carbamic acid tert-butyl ester.

20

¹H-NMR (CDCl₃): δ 1.05, 1.31, 1.56 (three s, 9H); 2.28-3.37 (several m, 13 H); 5.04, 5.17, 5.29, 5.48 (four dd, 2H); 7.05-7.79 (m, 12 H).

(2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide:

25

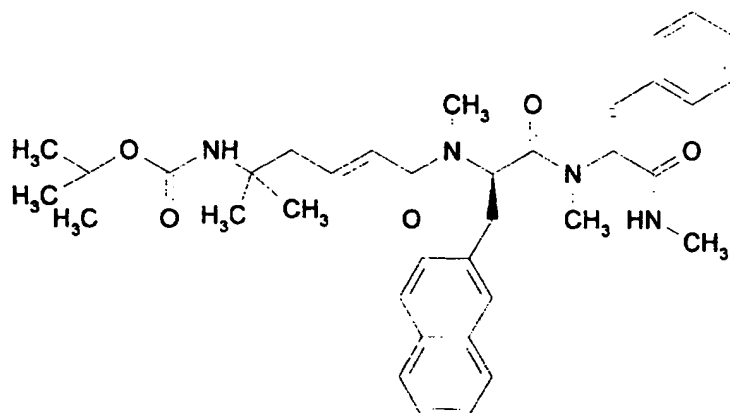


Step H: N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenyl-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester (600 mg, 1.19 mmol) was stirred in trifluoroacetic acid/methylene chloride (1:1, 5 mL) for 10 min and the volatiles were removed in vacuo. The residue was stripped with diethylether (2 x 5 mL) and dissolved in methanol (2 mL) and mixed with sodium hydrogen carbonate (10 mL) and ethylacetate (15 mL). The organic phase was separated and dried (magnesium sulfate) to afford 420 mg of (2R)-N-methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide.

¹H-NMR (CDCl₃): (selected values) δ 1.69 (s, 3H); 2.08 (d, 3H); 2.54 (s, 3H); 2.76 (dd, 1H); 2.92 (dd, 1H); 3.12 (dd, 1H); 3.31 (dd, 1H); 3.72 (dd, 1H); 4.95 (q (br), 1H); 5.50 (dd, 1H).

15

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester:



Step I: (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (200 mg, 0.82 mmol), 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol) and 1-ethyl-3-(3-
 5 dimethylaminopropyl)-carbodiimide hydrochloride (173 mg, 0.90 mmol) were dissolved in a mixture of methylene chloride (10 mL) and N,N-dimethylformamide (1 mL) and stirred for 15 min. N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (332 mg, 0.82 mol) dissolved in methylene chloride (5 mL) and diisopropylethylamine (0.14 mL) were added and
 10 the mixture was stirred overnight under nitrogen atmosphere. The mixture was diluted with methylene chloride (50 mL), washed with water (50 mL), sodium hydrogen carbonate (30 mL, saturated), and sodium hydrogensulfate (30 mL, 5%). The phases were separated and the organic phase was dried with magnesium sulfate and evaporated in vacuo. The residue was chromatographed (silica, 2 x 40
 15 cm) to afford 450 mg of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)-carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): (selected values) d 1.20, 1.22, 1.24, 1.30, 1.41, 1.55 (six s, 15 H),
 20 4.30, 4.40 (two s (br), 1H); 5.08, 5.18, 5.32, 5.60, 5.87 (five dd, 2H); 6.05 (dd, 1H); 6.75 (m, 1H).

Step J: ((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid
 25 tert-butyl ester (403 mg, 0.63 mmol) was stirred in a mixture of trifluoroacetic acid

(4mL) and methylene chloride (4 mL) for 10 min. The volatiles were removed in vacuo and the crude product was chromatographed on silica (400g) using a mixture of methylene chloride, ethanol and ammonia (25% in water) (80/18/2) as eluent. The isolated product was dissolved in 3M hydrochloric acid in ethyl acetate and
5 evaporated, then redissolved in methylene chloride and evaporated twice to afford 140 mg of the title compound.

¹H-NMR (CDCl₃): d 1.05, 1.10, 1.15, 1.16 (four s, 6H); 2.07 (s (br); 3H); 5.12, 5.32, 5.40, 5.60, 5.91 (five dd, 2H); 6.05, 6.14 (two d, 1H); 6.80 (m, 1H)

10

HPLC: R_t = 29.02 min (Method A1)

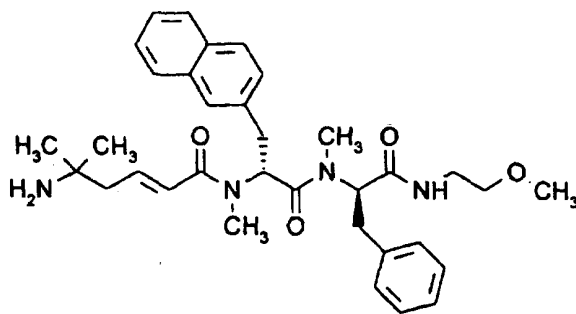
ESMS: m/z = 529 (100%)(M+H)⁺

15

Example 2:

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((2-methoxyethyl)-
carbamoyl)-2-phenylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

20



This compound was prepared analogously to example 1. 2-methoxyethylamine was
25 substituted for methylamine in step E.

¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) d 1.05; 1.10 (two d, 6H),

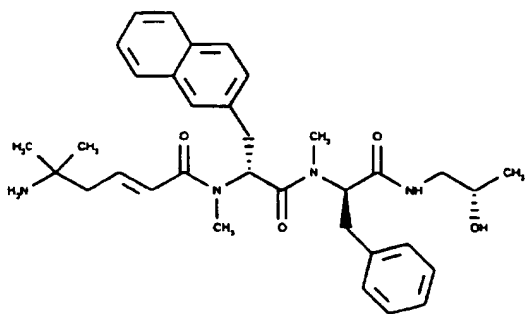
3.34 (s, 3H), 6.02 (d, 1H)

HPLC: R_t = 30.47 min (Method A1)

5 PDMS: m/z = 573.3 (100%) (M+H)⁺

Example 3:

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((2S)-2-hydroxy-
10 propylcarbamoyl)-2-phenylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



15

This compound was prepared analogously to example 1. (S)-2-hydroxypropylamine was substituted for methylamine in step E.

¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) d 3.90 (m, 1H); 5.55 (dd,
20 1H); 5.58 (d, 1H)

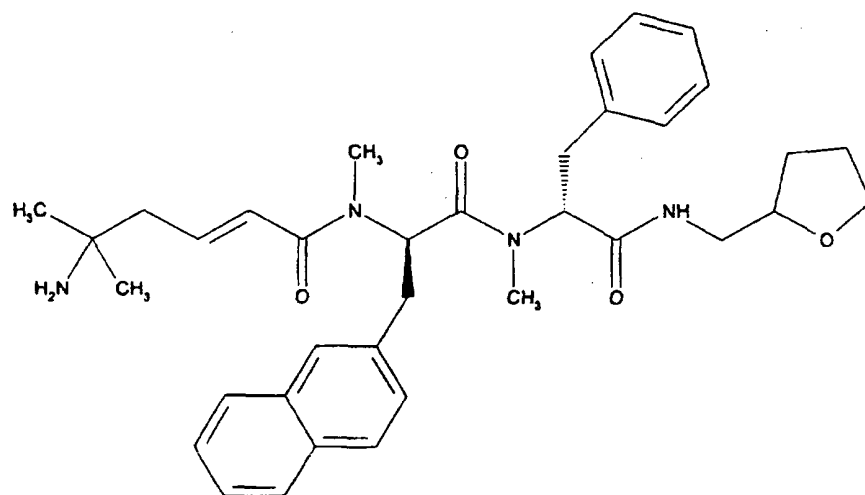
HPLC: R_t = 29.03 min (Method A1)

PDMS: m/z = 573.5 (100%)(M+H)⁺

25

Example 4:

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)-carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)amide:



- 10 This compound was prepared analogously to example 1. 2-(methyl-amino)tetrahydrofuran was substituted for methylamine in step E.

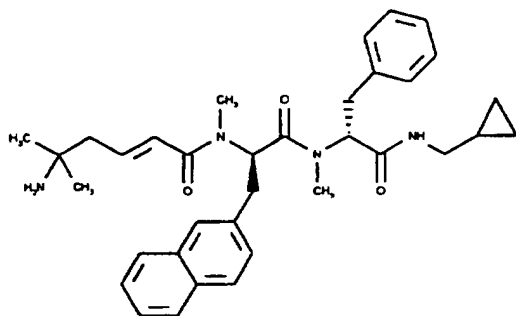
¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) δ 1.06, 1.09 (two d, 6H); 2.78 (d, 2H); 5.25-5.62 (m, 2H); 6.05 (m, 1H)

15

HPLC: R_t = 33.65 min (method A1)

Example 5:

(2E)-5-Amino-5-methylhex-2-enoic acid N-(((1R)-1-(((1R)-1-((cyclopropylmethyl)-carbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



5

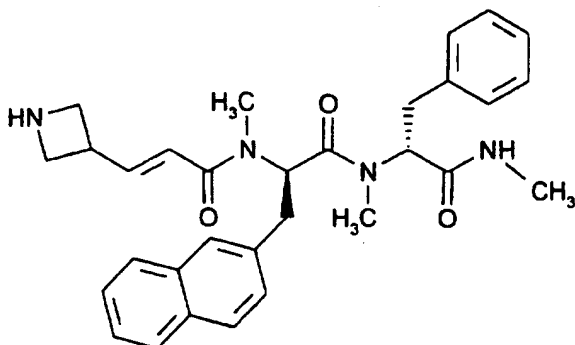
This compound was prepared analogously to example 1. Cyclopropylmethylamine
10 was substituted for methylamine in step E.

¹H-NMR (CDCl₃) (selected peaks, mixture of rotamers) δ 0.08-0.20 (m, 2H); 1.05;
1.15 (two s, 6H); 6.02, 6.05 (two d, 1H)

15 HPLC: R_t = 35.7 min (Method A1)

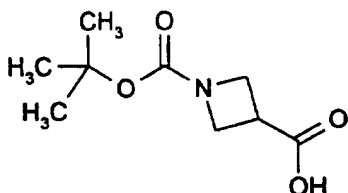
Example 6

20 (2E)-3-(Azetidin-3-yl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)acrylamide:



3-Carboxyazetidine-1-carboxylic acid tert-butyl ester.

5

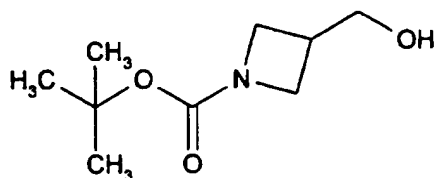


Azetidine-3-carboxylic acid (10.0 g; 98.9 mmol) was dissolved in tetrahydrofuran (120 mL) and water (20 mL). An aqueous solution of sodium hydroxide (10 mL; 1 N) was added. Di-tert butyl dicarbonate (25.9 g; 118.7 mmol) was dissolved in tetrahydrofuran (80 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred for 12 hours at room temperature and evaporated in vacuo. To the residue was added water (100 mL) and an aqueous solution of sodium hydroxide (100 mL; 1N) and the aqueous phase was extracted with diethyl ether (2 x 100 mL). The aqueous phase was acidified with an aqueous solution of sodium hydrogensulfate (1 M) until pH 2. Diethyl ether (200 mL) was added and the organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 20 g of 3-carboxyazetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ 1.43 (s, 9H); 3.37 (p, 1H); 4.14 (d, 4H); 10.05 (s, 1H).

20

3-Hydroxymethylazetidine-1-carboxylic acid tert-butyl ester.

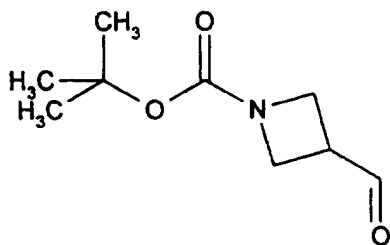


1-Carboxyazetidine-1-carboxylic acid tert-butyl ester (5.0 g; 24.8 mmol) was dissolved in dry tetrahydrofuran. Triethylamine (4.1 mL; 29.8 mmol) was added and
5 the reaction mixture was cooled to 0°C. Ethyl chloroformate (2.4 mL; 24.8 mmol) was added and the reaction mixture was stirred for 40 min at 0°C. The reaction mixture was filtered and the filter cake was washed with dry tetrahydrofuran (30 mL). The combined filtrates were cooled to 0°C and lithium borohydride (2.0 M in tetrahydrofuran; 31 mL; 62.1 mmol) was added dropwise to the reaction mixture
10 and it was then heated to room temperature and stirred for 12 hours. The reaction mixture was cooled to 0°C and methanol (10 mL) was added dropwise. An aqueous solution of sodium hydrogen carbonate (100 mL; 10 %) was added and the reaction mixture was extracted with ethyl acetate (4 x 100 mL). The combined organic phases were washed with a saturated solution of sodium hydrogen carbonate (100
15 mL), dried (magnesium sulfate) and evaporated in vacuo to afford 3.43 g of 3-hydroxymethylazetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.43 (s, 9H); 2.7 (p, 1H); 3.63-3.70 (m, 2H), 3.74 (d, 1H); 3.88 (d, 1H); 3.9-4.0 (m, 2H).

20

3-Formylazetidine-1-carboxylic acid tert-butyl ester.



25

Oxalyl chloride (2.1 mL; 24.0 mmol) was dissolved in methylene chloride (30 mL) and cooled to -78°C. Dimethyl sulfoxide (2.3 mL; 32.0 mmol) was added. A solution of 3-hydroxymethylazetidine-1-carboxylic acid tert-butyl ester (3.0 g; 16.0 mmol) in methylene chloride (20 mL) was added dropwise to the reaction mixture.

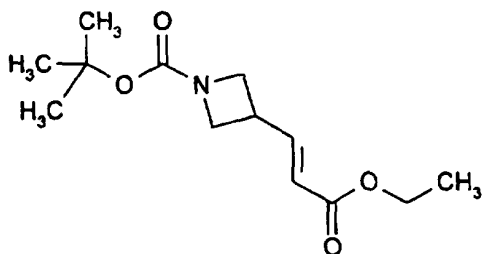
5 Triethyl amine (11.1 mL; 80.1 mmol) was added and the reaction mixture was heated to room temperature. Methylene chloride (200 mL) and hydrochloric acid (200 mL; 1 N) was added. The aqueous phase was extracted with methylene chloride (100 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate (100 mL), dried (magnesium sulfate) and evaporated

10 in vacuo. The residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/heptane (4:1) as eluent to afford 1.11 g of 3-formylazetidine-1-carboxylic acid tert-butylester.

¹H-NMR (CDCl₃) δ : 1.43 (s, 9H); 3.37 (p, 1H); 4.05-4.15 (m, 4H); 9.82 (s, 1H).

15

3-((E)-2-Ethoxycarbonylvinyl)azetidine-1-carboxylic acid tert-butylester:



20 Triethyl phosphonoacetate (1.9 mL; 9.72 mmol) was dissolved in tetrahydrofuran (30 mL). Potassium tert-butoxide (1.1 g; 9.72 mmol) was added portionwise. 3-Formylazetidine-1-carboxylic acid tert-butyl ester (1.0 g; 5.40 mmol) was dissolved in tetrahydrofuran (6 mL) and added to the reaction mixture. The reaction mixture was stirred for 1 hour at room temperature. Ethyl acetate (100 mL) and

25 hydrochloric acid (100 mL; 1 N) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL) and the combined organic phases were washed with saturated sodium hydrogen carbonate (100 mL),

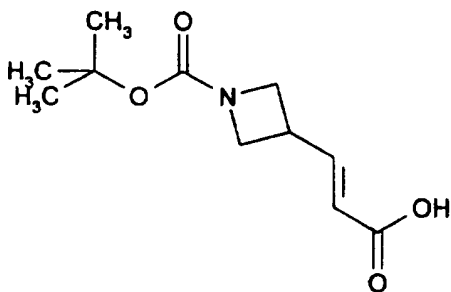
dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/heptane (1:1) as eluent to afford 1.0 g of 3-((E)-2-ethoxycarbonylvinyl)azetidine-1-carboxylic acid tert-butyl ester.

5

¹H-NMR (CDCl₃) δ : 1.24 (t, 3H); 1.48 (s, 9H); 3.22-3.32 (m, 1H); 3.75 (dd, 2H); 4.08 (t, 2H); 4.15 (q, 2H); 5.8 (d, 1H); 7.02 (dd, 1H).

3-((E)-2-Carboxyvinyl)azetidine-1-carboxylic acid tert-butyl ester:

10

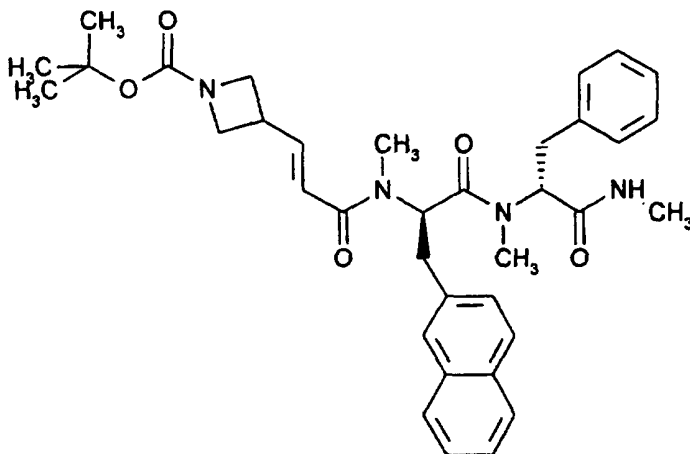


3-((E)-2-Ethoxycarbonylvinyl)azetidine-1-carboxylic acid tert-butyl ester (0.95 g; 3.72 mmol) was dissolved in 1,4-dioxane (15 mL). Lithium hydroxide (0.098 g; 4.1 mmol) and water (10 mL) were added. The reaction mixture was stirred for 12 hours at room temperature. Water (70 mL) was added and the reaction mixture was washed with tert-butyl methyl ether (70 mL) and the phases were separated. The aqueous phase was adjusted to pH 2 with an aqueous solution of sodium hydrogensulfate (10 %) and extracted with tert-butyl methylether (3 x 70 mL). The combined organic phases were dried (magnesium sulfate) and the solvent evaporated in vacuo to afford 0.76 g of 3-((E)-2-carboxyvinyl)azetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.43 (s, 9H); 3.31-3.42 (m, 1H); 3.84 (dd, 2H); 4.16 (t, 2H); 5.88 (d, 1H); 7.18 (dd, 1H).

3-(2-(Methyl-((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-

2-(2-naphthyl)ethyl)carbamoyl)vinyl)azetidine-1-carboxylic acid tert-butyl ester:



- 5 3-((E)-2-Carboxyvinyl)azetidine-1-carboxylic acid tert-butyl ester (0.28 g; 1.24 mmol) was dissolved in methylene chloride (3 mL). 1-Hydroxy-7-azabenzotriazole (0.17 g; 1.24 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g; 1.36 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. N-Methyl-2-methylamino-N-(1-(methyl-carbamoyl)-
- 10 2-phenylethyl)-3-(2-naphthyl)propionamide (0.50 g; 1.24 mmol) (prepared as in example 1) was dissolved in methylene chloride (3 mL) and added to the reaction mixture. Ethyldiisopropylamine (0.21 mL; 1.24 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (20 mL) was added and the reaction mixture was washed with water (10 mL), an aqueous
- 15 solution of sodium hydrogen sulfate (10 mL; 10 %), an aqueous solution of sodium hydrogen carbonate (10 mL; sat.) and water (10 mL). The organic phase was dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (2,5 x 20 cm) using 2.5%(7% ammonia in ethanol) in methylene chloride as eluent to afford 0.49 g of 3-((E)-2-(methyl((1R)-1-(methyl((1R)-1-
- 20 (methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)vinyl)azetidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ 1.41, 1.45 (two s, 9H); 1.55, 1.58 (two s, 3H); 2.21 (d, 1H); 2.54 (s, 1H); 2.72-2.81 (m, 3H); 2.83-2.96 (m, 1H); 3.0 (d, 3H); 3.02-3.42 (m, 3H); 3.68-

3.82 (m, 2H); 4.06 (q, 1H); 4.14 (q, 1H); 5.11, 5.31 (two m, 1H); 5.58, 5.88 (two dd, 1H); 6.03 (d, 1H); 6.88, 6.91 (two dd, 1H); 7.0-7.23 (m, 5H); 7.3-7.58 (m, 3H); 7.65-7.81 (m, 3H).

5 3-((E)-2-(Methyl((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)vinyl)azetidine-1-carboxylic acid tert-butyl ester (0.45 g; 0.73 mmol) was dissolved in methylene chloride (2 mL). Trifluoroacetic acid (2 mL) was added and the reaction mixture was stirred for 7 min. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen
10 carbonate/sodium carbonate (50 mL; pH 9) and sodium carbonate were added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.29 g of the title compound.

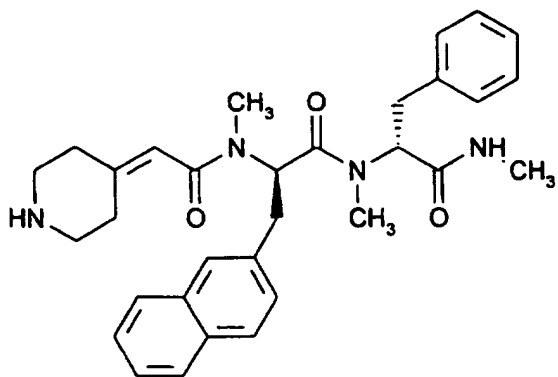
¹H-NMR (CDCl₃) δ (selected peaks) : 2.25, 2.26, 2.28 (three s, 3H); 5.12, 5.31,
15 5.59, 5.88 (four dd, 2H); 6.00 (dd, 1H; J₁=15 Hz; J₂=2.5 Hz); 6.91 (m, 1H).

ESMS: m/z 513.2 (M+H)⁺

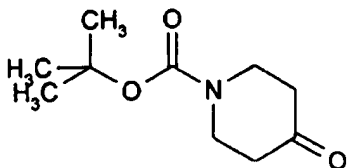
HPLC: t_r = 29.40 min (A1)

20 Example 7

(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(methyl((piperidin-4-ylidene)acetyl)amino)-3-(2-naphthyl)propionamide:



4-Oxopiperidine-1-carboxylic acid tert-butyl ester:



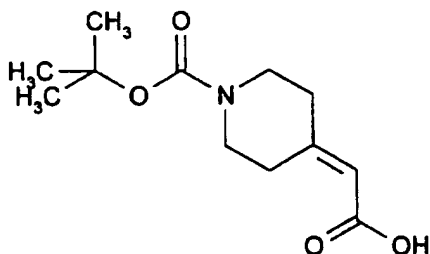
5

Piperidin-4-one hydrochloride (10.0 g; 74.3 mmol) was dissolved in tetrahydrofuran (100 mL) and an aqueous solution of sodium hydroxide (74 mL; 74.3 mmol; 1 N) was added. Di-tert-butyl dicarbonate (19.5 g; 89.2 mmol) was dissolved in tetrahydrofuran (50 mL) and added dropwise. The reaction mixture was stirred for
10 12 hours at room temperature and evaporated in vacuo. The residue was extracted with ethyl acetate (3 x 100 mL). The combined organic phases were washed with an aqueous solution of sodium hydrogen sulfate (100 mL; 10 %), dried (magnesium sulfate) and evaporated. The residue was crystallised from heptane and dried in vacuo to afford 10.9 g of 4-oxopiperidine-1-carboxylic acid tert-butyl ester.

15

¹H-NMR (CDCl₃) δ : 1.50 (s, 9H); 2.44 (t, 4H); 3.71 (t, 4 H).

20 4-Carboxymethylenepiperidine-1-carboxylic acid tert-butyl ester:



4-Oxopiperidine-1-carboxylic acid tert-butyl ester (8.0 g; 40.2 mmol) was dissolved
25 in toluene (80 mL). Carboethoxymethylene triphenylphosphorane (17.5 g; 50.2

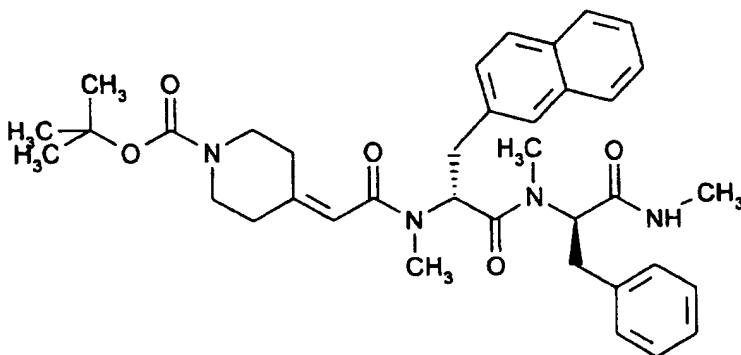
mmol) was added and the reaction mixture was heated 12 hours at reflux. The reaction mixture was evaporated in vacuo and the residue was chromatographed on silica (4.5 x 30 cm) using diethyl ether/heptane (1:1) as eluent to afford 9.5 g (35.7 mmol) of 4-Ethoxycarbonylmethylenepiperidine-1-carboxylic acid tert-butyl ester, which was dissolved in 1,4-dioxane and cooled to 0°C. Lithium hydroxide (2.73 g; 114 mmol) was dissolved in water (20 mL) and added. The reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (200 mL) and water (100 mL) was added. Sodium hydrogen sulfate (10 %; aqueous solution) was added to pH 2. The organic phase was washed with water (100 mL), dried (magnesium sulfate) and evaporated in vacuo to afford 5.49 g of 4-carboxymethylenepiperidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.47 (s, 9H); 2.31 (t, 2H), 2.94 (t, 2H); 3.50 (dt, 4H); 5.75 (s, 1H); 10.75 (s, 1H).

15

4-((N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methylene)piperidine-1-carboxylic acid tert-butyl ester:

20



4-Carboxymethylenepiperidine-1-carboxylic acid tert-butyl ester (0.60 g; 2.45 mmol) was dissolved in methylene chloride (50 mL) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g; 1.36 mmol) was added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-(methyl-carbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (0.5 g;

1.24 mmol, prepared as in example 1) was added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (50 mL; 10 %), an aqueous solution of sodium hydrogen carbonate (50 mL; sat.), dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (2 x 20 cm) using ethyl acetate as eluent to afford 0.270 g of 4-((N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methyl-carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methylene)piperidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.42 (s, 3H); 1.45 (s, 3H); 1.52, 1.55 (two s, 9H); 2.05-2.18 (m, 1H); 2.34-2.42 (m, 2H); 2.71-2.80 (m, 3H); 2.80-2.89 (m, 1H); 2.90-3.01 (m, 3H); 3.02-3.36 (m, 3H); 5.16, 5.36 (two m, 1H); 5.57, 5.90 (two t, 1H); 6.90-7.25 (m, 6H); 7.28-7.53 (m, 3H); 7.61-7.82 (m, 3H).

4-((N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methylene)piperidine-1-carboxylic acid tert-butyl ester (0.27 g; 0.43 mmol) was dissolved in methylene chloride (8 mL) and trifluoroacetic acid (8 mL) was added. The reaction mixture was stirred for 10 min. Methylene chloride (30 mL) and an aqueous solution of sodium hydrogen carbonate (10 mL; saturated) were added. Solid sodium hydrogen carbonate was added to pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.17 g of the title compound.

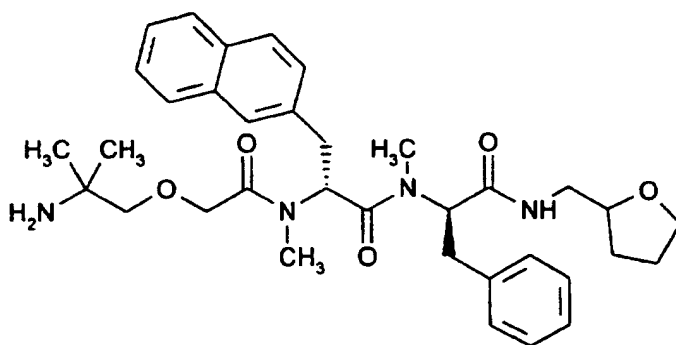
¹H-NMR (CDCl₃) δ (rotamers, selected peaks): 5.18; 5.38; 5.58; 5.90 (four dd, 2H); 5.49, 5.52 (two s, 1H)

ESMS: m/z 527.4 (M+H)⁺

HPLC: t_r = 28.62 min (Method A1)

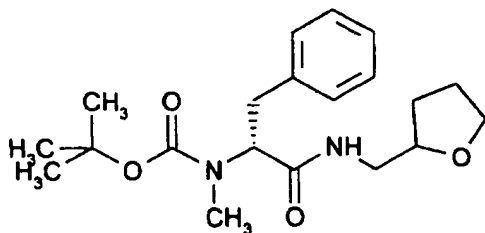
Example 8

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-3-(2-naphthyl)-N-(((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide:



10

Methyl-(((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamic acid tert-butyl ester:

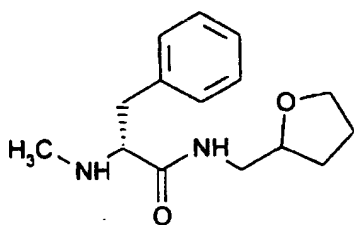


15 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-phenylpropionic acid (5.0 g; 17.9 mmol) was dissolved in methylene chloride (50 mL). 1-Hydroxybenzotriazole (2.42 g; 17.9 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.58 g; 18.8 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. ((Tetrahydrofuran-2-yl)methyl)amine (1.72 g; 17.1 mmol) and
20 diisopropyl- ethylamine (3.2 mL; 18.8 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (200 mL) was added and the reaction mixture was washed with water (100 mL), an aqueous

solution of sodium hydrogen sulfate (10 %, 100 mL), an aqueous solution of sodium hydrogen carbonate (saturated, 100 mL), water (100 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (2:1) as eluent to afford 5.62 g of methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 1.28; 1.38 (two s, 9H); 1.40-1.57 (m, 1H); 1.76-2.01 (m, 3H); 2.70-2.80 (m, 3H); 2.86-2.96 (m, 1H); 3.15-3.61 (m, 3H); 3.67-3.75 (m, 1H); 3.76-3.85 (m, 1H); 3.86-3.99 (m, 1H); 4.72; 4.92 (two m, 1H); 6.26; 6.4 (two m, 1H); 7.14-7.29 (m, 5H).

(2R)-2-Methylamino-3-phenyl-N-((2-tetrahydrofuranyl)methyl)propionamide:

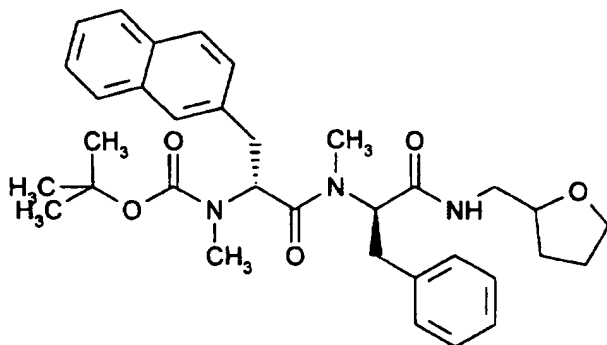


Methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamic acid tert-butyl ester (5.5 g; 15.2 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid (20 mL) was added. The reaction mixture was stirred for 1 hour at room temperature. Methylene chloride (100 mL) and an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9, 50 mL) were added and solid sodium hydrogen carbonate was added until pH 8. The aqueous phase was extracted with methylene chloride (100 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to afford 3.62 g of (2R)-2-Methyl-amino-3-phenyl-N-((2-tetrahydrofuranyl)methyl)propionamide.

¹H-NMR (CDCl₃) δ : 1.46-1.57 (m, 1H); 1.62 (s, 1); 1.82-2.01 (m, 3H); 2.29 (d, 3H); 2.65-2.74 (m, 1H); 3.16-3.27 (m, 3H); 3.49-3.58 (m, 1H); 3.7-3.78 (m, 1H); 3.8-3.88 (m, 1H); 3.9-3.98 (m, 1H); 7.19-7.34 (m, 5H); 7.43 (s, 1H).

Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)-
 carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamamic acid tert-butyl ester:

5

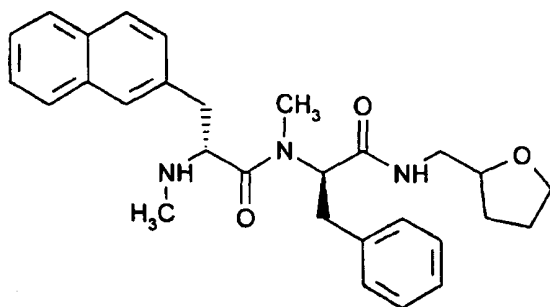


(2R)-2-(tert-Butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (4.14 g;
 12.58 mmol) was dissolved in methylene chloride (40 mL). 1-Hydroxy-7-
 azabenzotriazole (1.71 g; 12.6 mmol) and N-(3-dimethylaminopropyl)-N'-
 10 ethylcarbodiimide hydrochloride (2.52 g; 13.2 mmol) were added and the reaction
 mixture was stirred for 15 min at room temperature. (2R)-2-Methylamino-3-phenyl-
 N-((2-tetrahydrofuranyl)methyl)propionamide (3.0 g; 11.4 mmol) and
 diisopropylethylamine (2.15 mL; 12.6 mmol) were added. The reaction mixture was
 stirred for 12 hours at room temperature. Methylene chloride (200 mL) was added.
 15 The reaction mixture was washed with water (200 mL), an aqueous solution of
 sodium hydrogen carbonate/sodium carbonate (pH 9, 100 mL), an aqueous
 solution of sodium hydrogen sulfate (10 %, 100 mL), water (100 mL) and dried
 (magnesium sulfate). The solvent was removed in vacuo and the residue was
 chromatographed on silica (4 x 40 cm) using ethyl acetate/heptane (1:1) as eluent
 20 to afford 4.27 g of methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydro-furan-2-
 yl)methyl)-carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamamic acid tert-butyl
 ester.

¹H-NMR (CDCl₃) δ : 1.01 (s, 2H); 1.24 and 1.27 (two s, 9H); 1.54-1.64 (m, 1H);
 25 1.65-1.99 (m, 2H); 2.24 (t, 2H); 2.7-2.8 (m, 1H); 2.82; 2.88 (two d, 3H); 2.95 (s, 3H);

3.00-3.44 (m, 2H); 2.45-2.98 (m, 3H); 4.96-5.10 (m, 1H); 5.30-5.45 (m, 1H); 5.95; 6.17 (two m, 1H); 7.02-7.10 (m, 1H); 7.11-7.23 (m, 4H); 7.34-7.47 (m, 3 H); 7.65 (s, 1H); 7.68-7.8 (m, 4H).

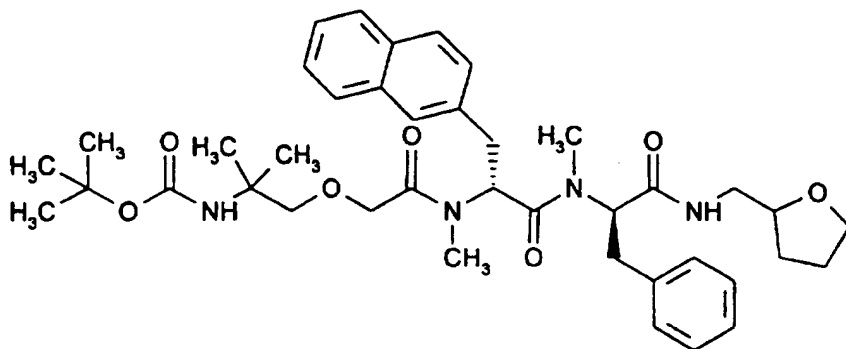
- 5 (2R)-N-Methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)propionamide:



- Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)-
 10 carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester. (4.2 g; 7.32 mmol) was dissolved in methylene chloride (20 mL) and trifluoroacetic acid (20 mL) was added. The reaction mixture was stirred for 15 min at room temperature. Methylene chloride (100 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9, 100 mL) and solid sodium hydrogen
 15 carbonate were added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 3.5 g of (2R)-N-methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)propionamide.

20

(1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)-ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butyl ester:



(2-tert Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.5 g; 2.06 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.2 g; 1.51 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.30 g; 1.58 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)propionamide (0.65 g; 1.37 mmol) and diisopropylethylamine (0.26 mL; 1.51 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (100 mL) was added. The reaction mixture was washed with an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate (sat; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was filtered through silica to afford 0.76 g of (1,1-dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ : 0.89-0.95 (m, 3H); 1.1; 1.15 (two s, 3H); 1.41; 1.43 (two s, 9H); 1.68-2.0 (m, 4H); 2.22 (s, 1H); 2.26 (s, 1H); 2.82; 2.86 (two d, 3H); 2.88-2.97 (m, 2H); 2.99 (d, 3H); 3.06-3.36 (m, 3H); 3.45-3.95 (m, 5H); 5.05; 5.16 (two m, 1H); 5.33 (s, 1H); 5.37-5.5 (m, 1H); 5.81; 5.91 (two q, 1H); 6.89-7.1 (m, 2H); 7.13-7.24 (m, 4H); 7.34-7.47 (m, 3H); 7.63 (s, 1H); 7.69-7.79 (m, 3H).

(1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
 (((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-
 naphthyl)ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butyl ester (0.76 g; 1.08
 mmol) was dissolved in methylene chloride (5 mL) and trifluoroacetic acid (5 mL)
 5 was added. The reaction mixture was stirred for 10 min at room temperature.
 Methylene chloride (50 mL), an aqueous solution of sodium hydrogen
 carbonate/sodium carbonate (pH 9; 50 mL) and solid sodium hydrogen carbonate
 was added to the reaction mixture until pH 8. The aqueous phase was extracted
 with methylene chloride (2 x 50 mL) and the combined organic layers were dried
 10 (magnesium sulfate) and evaporated in vacuo to afford 0.6 g of the title compound.

¹H-NMR (CDCl₃) d (rotamers; selected peaks) : 1.00; 1.02; 1.03; 1.09 (four s; 6H);
 5.07; 5.15; 5.78; 5.97 (four dd, 1H); 5.42 (m; 1H).

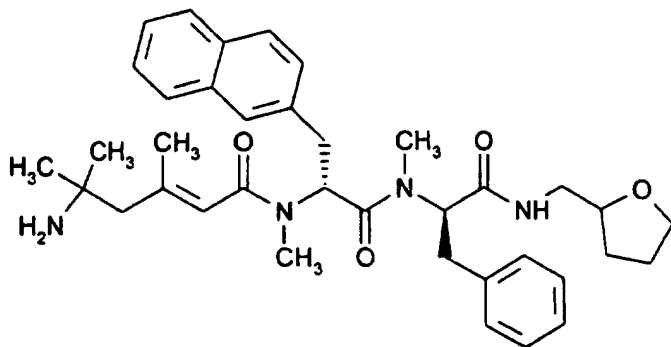
15 ESMS: m/z 602.9 (M+H)⁺

HPLC: R_t = 33.30 (Method A1)

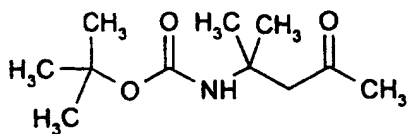
Example 9

20

(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-
 2-phenyl-1-(((2-tetrahydrofuranyl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-
 naphthyl)ethyl)amide:



(1,1-Dimethyl-3-oxobutyl)carbamic acid tert-butylester:



5

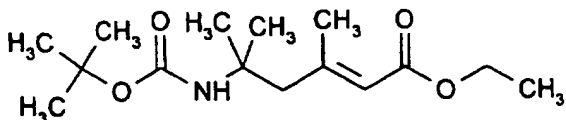
Diacetonamine hydrogen oxalate (30.0 g; 146 mmol) was suspended in tetrahydrofuran (400 mL). An aqueous solution of sodium hydroxide (1 N; 146 mL) was added. Di-tert-Butyl dicarbonate (38.3 g; 175 mmol) was dissolved in tetrahydrofuran (100 mL) and added dropwise to the reaction mixture. The reaction mixture was stirred for 2 hours at room temperature. Sodium hydroxide (1 N; 146 mL) was added and the reaction mixture was stirred for 12 hours at room temperature. Water (200 mL) and ethyl acetate (200 mL) were added. The aqueous phase was extracted with ethyl acetate (4 x 200 mL). The combined organic phases were dried (magnesium sulfate) and the solvent was removed in vacuo. The residue was chromatographed on silica (6 x 40 cm) using ethyl acetate/heptane (1:3) as eluent to afford 28.4 g of (1,1-dimethyl-3-oxobutyl)carbamic acid tert-butyl ester.

15

¹H-NMR (CDCl₃) δ 1.34 (s, 6H); 1.42 (s, 9H); 2.14 (s, 3H); 2.86 (s, 2H); 4.85 (s, 1H).

20

(E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid ethylester:



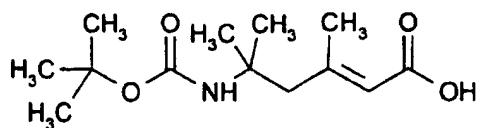
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Triethyl phosphono acetate (4.7 g; 20.9 mmol) was dissolved in tetrahydrofuran (36 mL). Potassium tert-butoxide (2.3 g; 20.9 mmol) was added and the reaction mixture was stirred for 40 min at room temperature.

(1,1-dimethyl-3-oxobutyl)carbamic acid tert-butylester (2.5 g; 11.6 mmol) was dissolved in tetrahydrofuran (15 mL) and added dropwise to the reaction mixture which was heated to reflux for 12 h. Ethyl acetate (100 mL) and hydrochloric acid (1 N; 100 mL) were added and the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with an aqueous solution of sodium hydrogen carbonate (saturated; 100 mL), dried (magnesium sulfate) and evaporated in vacuo. The residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (1:2) as eluent to afford 2.0 g of (E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid ethylester.

¹H-NMR (CDCl₃) δ 1.25 (t, 3H); 1.30 (s, 6H); 1.44 (s, 9H); 2.21 (s, 3H); 2.58 (s, 2H); 4.14 (q, 2H); 4.48 (s, 1H); 5.65 (s, 1H).

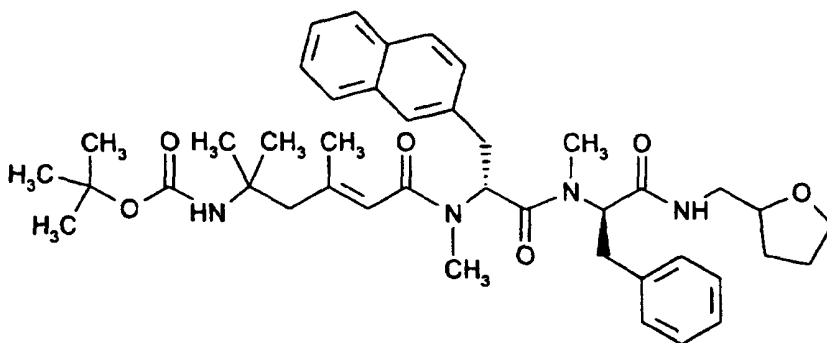
(2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid:



(E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid ethylester (1.95 g; 6.83 mmol) was dissolved in 1,4-dioxane (25 mL) and water (15 mL). Lithium hydroxide (0.18 g; 7.52 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Water (150 mL) and tert-butyl methyl ether (150 mL) was added. The aqueous phase was diluted with an aqueous solution of sodium hydrogensulfate (10 %) until pH 2,5 and extracted with tert-butyl methylether (3 x 100 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo. The residue was recrystallized from heptane (20 mL) to afford 0.6 g of (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid.

¹H-NMR (CDCl₃) δ 1.29 (s, 6H); 1.44 (s, 9H); 2.23 (s, 3H); 2.62 (s, 2H); 4.45 (s, 1H); 5.66 (s, 1H).

((3E)-1,1,3-Trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
 5 (((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)-
 ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester:



(2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid (0.3 g; 1.17 mmol)
 10 was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.12
 g; 0.85 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
 (0.17 g; 0.89 mmol) were added and the reaction mixture was stirred for 15 min at
 room temperature.

15 (2R)-N-Methyl-2-methylamino-3-(2-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-
 2-yl)methyl)carbamoyl)ethyl)propionamide (0.37 g; 0.78 mmol) and
 diisopropylethylamine (0.15 mL; 0.85 mmol) were added and the reaction mixture
 was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was
 added and the reaction mixture was washed with water (50 mL), an aqueous
 20 solution of sodium hydrogen carbonate (saturated; 30 mL), an aqueous solution of
 sodium hydrogen sulfate (10 %; 30 mL), water (30 mL), and dried (magnesium
 sulfate). The solvent was removed in vacuo and the residue was chromatographed
 on silica (2.5 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.21 g of
 ((3E)-1,1,3-trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
 25 (((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-

naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butylester.

¹H-NMR (CDCl₃)(rotamers; selected peaks) d : 1.15; 1.21; (two s; 6H); 1.30; 1.41 (two s; 9H).

5

((3E)-1,1,3-Trimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-
(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)-
carbamoyl)but-3-enyl)carbamic acid tert-butylester (0.20 g; 0.28 mmol) was
10 dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and
the reaction mixture was stirred for 6 min at room temperature. Methylene chloride
(50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH
9; 50 mL) and solid sodium hydrogen carbonate were added to the reaction mixture
to pH 8. The organic phase was dried (magnesium sulfate) and evaporated in
15 vacuo to afford 0.155 g of the title compound.

¹H-NMR (CDCl₃)(rotamers; selected peaks) d : 1.36; 1.41 (two s; 6H); 4.38; 5.12;
5.31; 6.25 (four m; 2H).

20

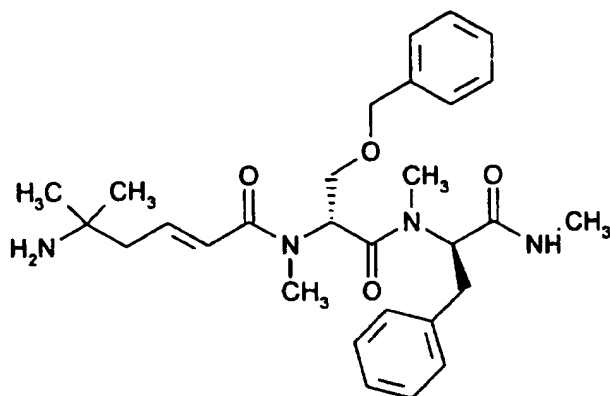
ESMS: m/z : 613.7 (M+H)⁺

HPLC: R_t = 34.47 (Method A1)

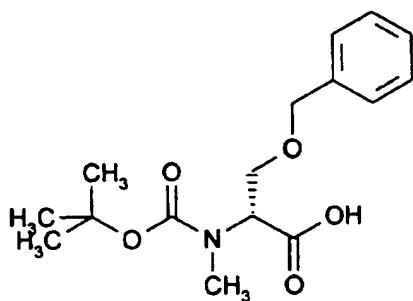
25

Example 10

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide:



(2R)-3-Benzoyloxy-2-(tert-butoxycarbonylmethylamino)propionic acid:



5

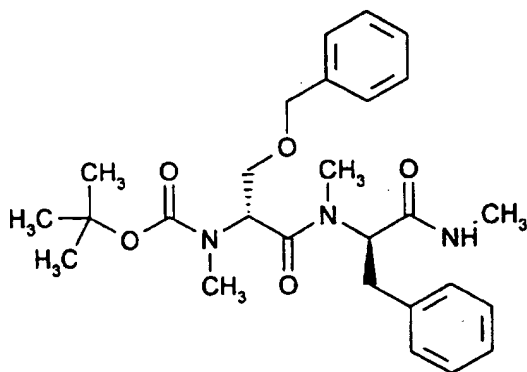
(2R)-3-Benzoyloxy-2-tert-butoxycarbonylaminopropionic acid (7.0 g; 23.7 mmol) was dissolved in dry tetrahydrofuran and iodomethane (11.9 mL; 189 mmol) was added. The reaction mixture was cooled to 0°C and sodium hydride (60 % in mineral oil)
 10 (2.73 g; 71 mmol) was added. The reaction mixture was left 3 days without stirring at 0°C. Citric acid (5 %) was added until pH 2.5. Tetrahydrofuran was removed in vacuo and the residue was extracted with methylene chloride (3 x 100 mL). The organic phase was dried (magnesium sulfate) and evaporated in vacuo. The residue was dissolved in diethyl ether (20 mL) and dicyclohexylamine (10 mL) and
 15 heptane (100 mL) were added. The reaction mixture was left 3 days without stirring at 0°C. The reaction mixture was filtered to afford 5.78 g of (2R)-3-benzoyloxy-2-(tert-butoxycarbonylmethylamino)propionic acid.

¹H-NMR (CDCl₃) δ 1.40; 1.42 (two s, 9H); 2.91; 2.97 (two s, 3H); 3.90, 3.91 (two s,

2H); 4.55 (two d, 2H); 3.83; 4.90 (two t, 1H); 7.25-7.38 (arom. 5H).

N-((1R)-2-Benzoyloxy-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)N-methylcarbamic acid tert-butyl ester:

5

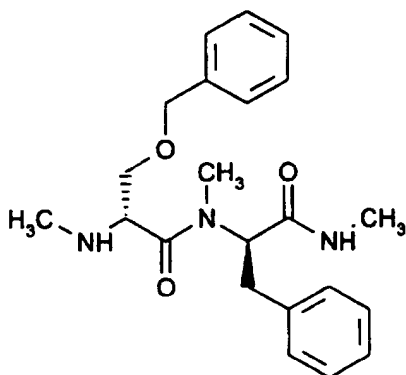


(2R)-3-Benzoyloxy-2-(tert-butoxycarbonylmethylamino)propionic acid (0.39 g; 1.25 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.16 g; 1.14 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
 10 hydrochloride (0.23 g; 1.20 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

N-methyl-2-methylamino-3-phenyl-propionamide (0.2 g; 1.04 mmol, prepared as in example 1) and diisopropylethylamine (0.2 mL; 1.14 mmol) were added and the
 15 reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was added. The reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate (saturated, 30 mL), an aqueous solution of sodium hydrogen sulfate (10 %, 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was
 20 chromatographed on silica (2.5 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.241 g of N-((1R)-2-benzoyloxy-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamic acid tert-butyl ester.

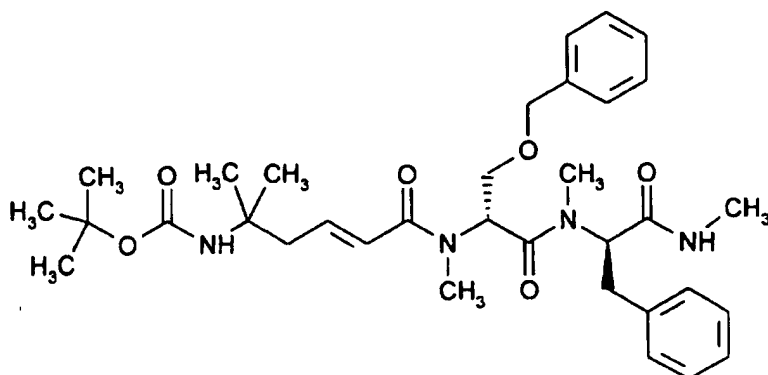
¹H-NMR (CDCl₃) (selected peaks) d 1.42; 1.45 (two s; 9H); 2.71; 2.78 (two d, 3H);
 25 2.84; 2.92 (two s; 3H); 4.11; 4.30 (two d; 1H); 4.43; 4.57 (two t; 1H)

(2R)-3-Benzoyloxy-N-methyl-2-(methylamino)-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)propionamide:



- 5 N-((1R)-2-Benzoyloxy-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)ethyl)N-methylcarbamic acid tert-butyl ester (0.23 g; 0.476 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred for 10 min at room temperature. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium
- 10 carbonate (pH 9) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.182 g of (2R)-3-Benzoyloxy-N-methyl-2-(methylamino)-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)propionamide.
- 15 ¹H-NMR (CDCl₃) (selected data for major rotamer) δ 2.18 (d, 3H); 2.92-2.95 (d and s, 6H); 3.31-3.45 (m, 4H); 3.65 (t, 1H); 4.45 (d, 1H); 4.48 (d, 1H); 4.65 (dd, 1H).

- ((3E)-4-(N-((1R)-2-Benzoyloxy-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic
- 20 acid tert-butyl ester:



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.12 g; 0.49 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.07 g; 0.49 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.1 g; 0.51 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-3-Benzyloxy-N-methyl-2-(methyl-amino)-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-propionamide (0.17 g; 0.44 mmol) and diisopropylethylamine (0.084 mL; 0.49 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was extracted with an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2.5 x 30 cm) using methylene chloride/ethyl acetate (1:1) as eluent to afford 0.275 g of ((3E)-4-(N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) (selected data for major rotamer) δ 1.25 (s, 3H); 1.27 (s, 3H); 1.41 (s, 9H); 2.05 (s, 3H); 2.78 (d, 3H); 3.07 (s, 3H); 4.32 (d, 1H); 4.41 (d, 1H); 5.05 (dd, 1H); 5.51 (dd, 1H); 6.30 (d; J=17 Hz; 1H); 6.79 (m, 1H).

((3E)-4-(N-((1R)-2-Benzyloxy-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic

acid tert-butyl ester (0.275 g; 0.452 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 7 min at room temperature. Methylene chloride (30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.13 g of the title compound.

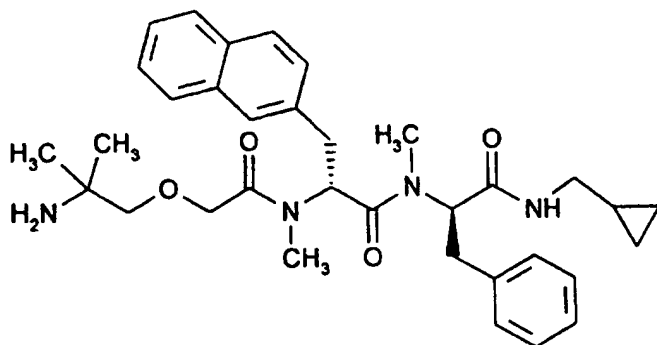
¹H-NMR (CDCl₃) (selected data for major rotamer) δ 1.27 (s, 3H); 1.28 (s, 3H); 2.84 (d, 3H); 2.95 (s, 3H); 3.08 (s, 3H); 4.32 (d, 1H); 4.40 (d, 1H); 5.12 (dd, 1H); 6.34 (d, J=18Hz, 1H).

ESMS: m/z 509.7 (M+H)⁺

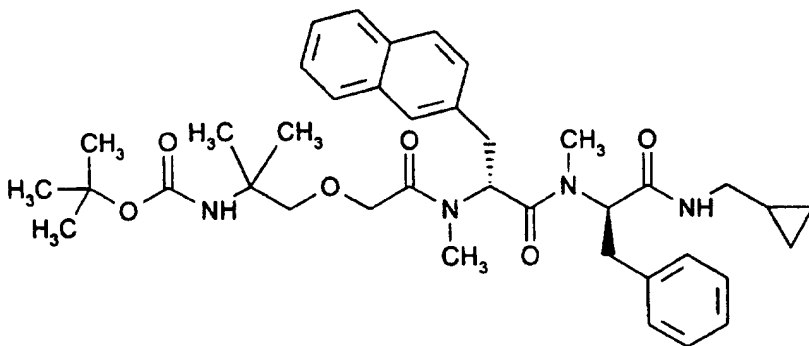
HPLC: R_t = 23.45 min (Method A1)

Example 11

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-1-((cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide:



(2-((N-((1R)-1-(N-((1R)-1-(Cyclopropylmethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester:



5

(2-tert-Butoxycarbonylamino-2-methylpropoxy) acetic acid (0.36 g; 1.49 mmol) was dissolved in methylene chloride (5 mL). 1-Hydroxy-7-azabenzotriazole (0.2 g; 1.49 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.3 g; 1.56 mmol) were added and the reaction mixture was stirred for 15 min at room

10 temperature.

(2R)-N-((1R)-1-((Cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.60 g; 1.35 mmol) and diisopropylethylamine (0.26 mL; 1.49 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was

15 added. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3.5 x 40 cm) using ethyl acetate/heptane (1:1) as eluent to afford 0.64 g of (2-((N-((1R)-1-(N-((1R)-1-((cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) (rotamers, selected peaks) δ : -0.11 (m 1H); 0.19 (m, 1H); 0.45 (m, 1H); 0.95; 1.17; 1.25; 1.27; 1.40; 1.43; 1.58 (seven s, 15H); 2.29; 2.81; 2.91;

25

3.03 (four s, 6H).

(2-((N-((1R)-1-(N-((1R)-1-((Cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester (0.64 g; 0.951 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (3 mL) was added. The reaction mixture was stirred for 5 min. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture to pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.48 g of the title compound.

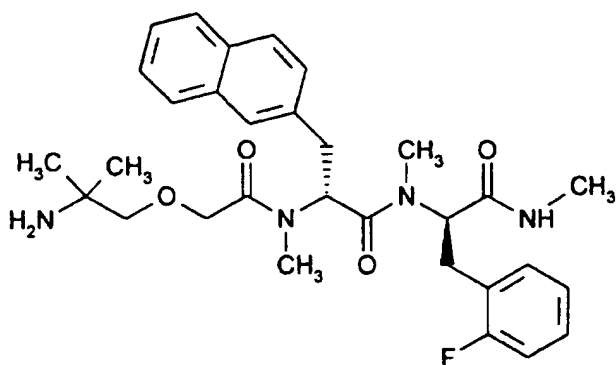
¹H-NMR (CDCl₃) (rotamers, selected peaks) δ : 0.55; 0.57; 0.80; 0.82 (four s, 6H); 2.09; 2.62; 2.75; 2.84 (four s; 6H); 3.68; 3.82 (two d, 2H together with a singlet at 3.69); 4.92; 5.22; 5.30; 5.38; 5.65 (five dd, 3H);

ESMS: m/z 572.0 (M+H)⁺

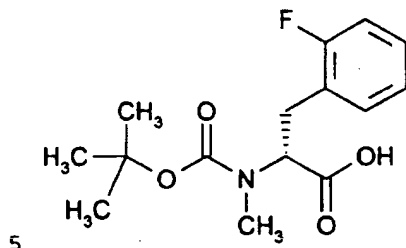
HPLC: R_t = 35.52 min (Method A1)

Example 12

(2R)-2-(((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:



(2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-fluorophenyl)propionic acid:



5

(The N-methylation in this and other examples in this invention may be performed as in Can. J. Chem. 1977, 55, 906).

10

(2R)-2-tert-Butoxycarbonylamino-3-(2-fluorophenyl)propionic acid (5.0 g; 17.5 mmol) was dissolved in dry tetrahydrofuran. Iodomethane (7.2 mL; 115 mmol) was added and the reaction mixture was cooled to 0°C. Sodium hydride (60% susp. in oil; 1.41 g; 42.0 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise. The ethyl acetate was removed in vacuo and the residue was diluted with ether (30 mL) and water (100 mL). The organic phase was extracted with an aqueous solution of sodium hydrogen carbonate (aqueous; 50 mL). To the combined aqueous layers was added citric acid (5 %) until pH 3 and ethyl acetate (3 x 50 mL) was added and the phases were separated. The combined organic layers were washed with water (2 x 50 mL), an aqueous solution of sodium

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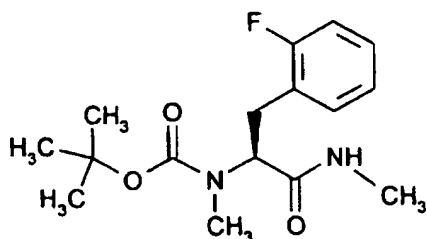
thiosulfate (5 %; 2 x 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was dissolved in diethyl ether (10 mL). Dicyclohexylamine (9.0 mL) was added. The reaction mixture was filtered to afford 5.57 g of (2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-2-

5 fluorophenyl)propionic acid as a dicyclohexylammonium salt.

¹H-NMR (CDCl₃) δ 1.27; 1.35 (two s, 9H); 2.21; 2.25 (two s, 3H); 3.03 (m, 2H); 4.26; 4.37 (two dd, 1H); 6.9-7.3 (arom 4H).

10

N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamic acid tert-butylester:



15

(2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-fluorophenyl)propionic acid as a dicyclohexylammonium salt (5.57 g; 18.73 mmol) was dissolved in methylene chloride (30 mL) and washed with an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL). The organic phase was dried (magnesium sulfate) and filtered. 1-

20 Hydroxybenzotriazole hydrate (2.53 g; 18.73 mmol) and N-(3-

dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (3.75 g; 19.6 mmol) were added to the filtrate and the mixture was stirred for 15 min at room temperature.

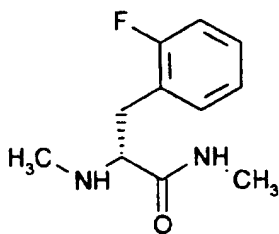
Methylamine (40% in methanol; 0.53 g; 17.0 mmol) and diisopropylethylamine (3.2 mL; 18.7 mmol) were added and the reaction mixture was stirred for 12 hours at

25 room temperature. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (50 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3.5 x 40 cm) using ethyl

acetate/heptane (2:1) as eluent to afford 2.4 g of N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamic acid tert-butyl ester.

H-NMR (CDCl₃) δ : 1.25; 1.35; 1.38 (three s, 9H); 2.74 (s, 3H); 2.75 (d, 3H); 2.80-
5 3.55 (m, 2H); 4.35; 4.82; 5.00; 5.12 (four dd; 6.9-7.3 (arom, 4H).

(2R)-3-(2-Fluorophenyl)-N-methyl-2-(methylamino)-propionamide:

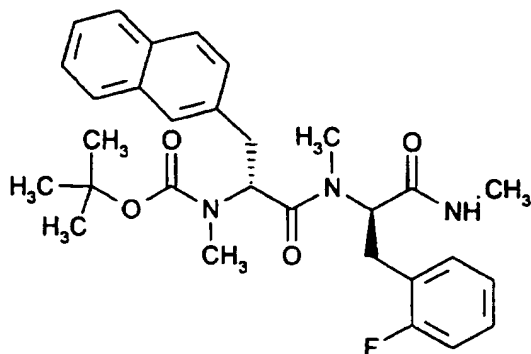


10 N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamic acid
tert-butylester (2.4 g; 7.73 mmol) was dissolved in methylene chloride.

Trifluoroacetic acid (10 mL) was added and the reaction mixture was stirred for 30
min at room temperature. Methylene chloride (30 mL), an aqueous solution of
sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen
15 carbonate (solid) were added to the reaction mixture until pH 8. The organic phase
was dried (magnesium sulfate) and evaporated in vacuo to afford 1.1 g of
(2R)-3-(2-fluorophenyl)-N-methyl-2-(methylamino)- propionamide.

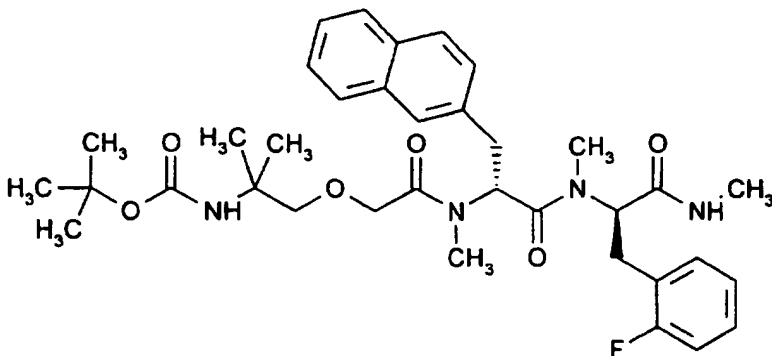
20 H-NMR (CDCl₃) δ 2.31 (s, 3H); 2.80 (d, 3H); 2.86 (dd, 1H); 3.17 (dd, 1H); 3.28
(dd, 1H); 7.0-7.30 (arom. 4H).

N-((1R)-1-(N-((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-
25 methylcarbamoyl)-2-(2-naphthyl)-ethyl)-N-methylcarbamic acid tert-butyl ester.



Tert-Butoxycarbonylaminoacetic acid (0.18 g; 2.39 mmol) was dissolved in methylene chloride (20 mL). 1-Hydroxybenzotriazole (0.32 g; 2.39 mmol) and N-(3-
 5 dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.55 g; 2.87 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.
 (2R)-3-(2-Fluorophenyl)-N-methyl-2-(methylamino)propionamide (1.0 g; 4.78 mmol) and diisopropylethylamine (0.9 mL; 5.26 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. A mixture of 2-(tert-
 10 butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (0.78 g; 2.39 mmol), 1-hydroxy-7-azabenzotriazole (0.33 g; 2.39 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.55 g; 2.87 mmol) were dissolved in methylene chloride (20 mL) and added to the reaction mixture. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added
 15 and the reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2.5 x 30 cm) using ethyl acetate/heptane (2:1) as eluent
 20 to afford 0.86 g of N-((1R)-1-(N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methyl-carbamic acid tert-butylester.

H-NMR (CDCl_3) (selected peaks, rotamers) δ : 1.34 (s, 9H); 2.35 (s, 3H); 2.78 (s, 3H); 5.03-5.45 (four m, 2H).



(2-tert-Butoxycarbonylamino-2-methylpropoxy) acetic acid (0.19 g; 0.78 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.12 g; 0.86 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.90 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-(((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.33 g; 0.78 mmol) and diisopropylethylamine (0.17 mL; 0.86 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 50 mL), water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.47 g of (2-((((1R)-1-(((1R)-2-(2-fluorophenyl)-1-methylcarbamoyl-ethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)methyl-carbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) (rotamers, selected peaks for major isomer) δ 1.03 (s, 3H); 1.06 (s, 3H); 2.78 (s, 3H); 2.80 (d, 3H); 3.98 (s, 3H); 4.95 (d, 1H); 5.00 (d, 1H); 5.70 (dd, 1H), 5.85 (dd, 1H).

(2-((((1R)-1-(((1R)-2-(2-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert-butyl ester (0.46 g; 0.707 mmol) was dissolved in methylene chloride (3 mL).

Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 8. The organic phase
 5 was dried (magnesium sulfate) and evaporated in vacuo to afford 0.275 g of the title compound.

H-NMR (CDCl_3) (selected peaks, rotamers) d : 0.76; 0.99 (two d, 6H); 2.30; 2.80 (two d, 3H); 2.47; 2.78; 2.94; 2.97 (four s, 6H); (3.90 (d), 3.94(s), 4.05 (d), 2H);
 10 5.27; 5.37; 5.67; 5.86 (four dd, 2H); 6.96-7.82 (arom. 12H).

PDMS : m/z 550.7 (M+H)⁺

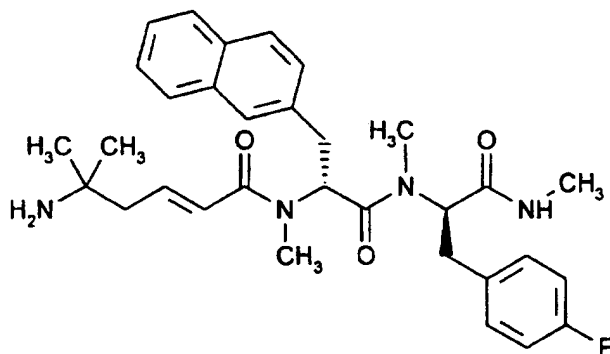
HPLC: R_t = 31.28 min (Method A1)

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Example 13

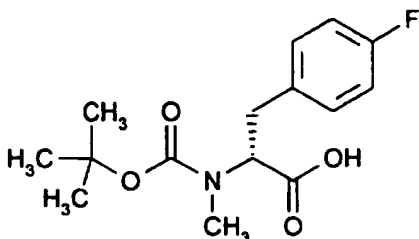
(2E)-5-Amino-5-methylhex-2-enoic acid (((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide:

20



(R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid:

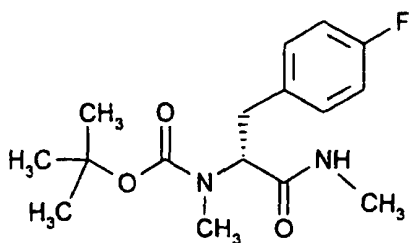
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2-tert-Butoxycarbonylamino-3-(4-fluorophenyl)propionic acid (5.0 g; 17.7 mmol) was dissolved in dry tetrahydrofuran. Iodomethane (8.8 mL; 141 mmol) was added and the reaction mixture was cooled to 0°C. Sodium hydride (2.1 g; 53.0 mmol) was slowly added and the reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise to the reaction mixture. The ethyl acetate was removed in vacuo and the residue was diluted with diethyl ether (30 mL) and water (100 mL). The organic phase was extracted with a saturated aqueous solution of sodium hydrogen carbonate (50 mL). Citric acid (5 %) was added to the combined aqueous phases until pH 3, which were then extracted with ethyl acetate (2 x 50 mL) and the phases were separated. The organic phase was washed with water (2 x 50 mL), an aqueous solution of sodium thiosulfate (5 %; 2 x 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was dissolved in diethyl ether (10 mL). Dicyclohexylamine (10 mL) was added. Methylene chloride (30 mL) was added and the mixture was heated until the precipitate was dissolved. Diethyl ether (20 mL) and heptane (20 mL) were added and the reaction mixture was left 12 hours without stirring. The reaction mixture was filtered to afford 5.7 g of (R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid as a dicyclohexylammonium salt.

¹H-NMR (CDCl₃) (mixture of rotamers) δ : 1.21; 1.31 (two s, 9H); 2.75; 2.84 (two s, 3H); 2.86-3.02 (m, 1H); 3.28-3.42 (m, 1H); 4.65; 4.85 (two dd, 1H); 6.85-7.00 (m, 2H); 7.10-7.25 (m, 2H).

((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester:



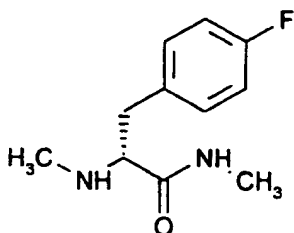
The dicyclohexylammoniumsalt of

- 5 (R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid (3.00 g; 10.1 mmol) was dissolved in methylene chloride (30 mL) and washed with an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL). The organic phase was dried (magnesium sulfate) and filtered. 1-Hydroxybenzotriazole (1.40 g; 10.1 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.0 g; 10.6 mmol) were added to the filtrate and the reaction mixture was stirred for 15 min at room temperature. Methylamine (40 % in methanol; 0.75 g; 9.17 mmol) and diisopropylethylamine (1.7 mL; 10.1 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (sat; 50 mL) and an
- 15 aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.06 g of ((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester.

20

¹H-NMR (CDCl₃) δ : 1.29; 1.37 (two s, 9H); 2.74 (s, 3H); 2.8 (s, 3H); 2.82-2.95 (m, 1H); 3.36-3.48 (m, 1H); 4.63; 4.86 (m, 1H); 5.89; 6.14 (two s, 1H); 6.9-7.0 (m, 2H); 7.1-7.21 (m, 2H).

- 25 (2R)-3-(4-Fluorophenyl)-N-methyl-2-(methylamino)propion-amide:



((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid

tert-butylester (1.0 g; 3.22 mmol) was dissolved in methylene chloride (5 mL).

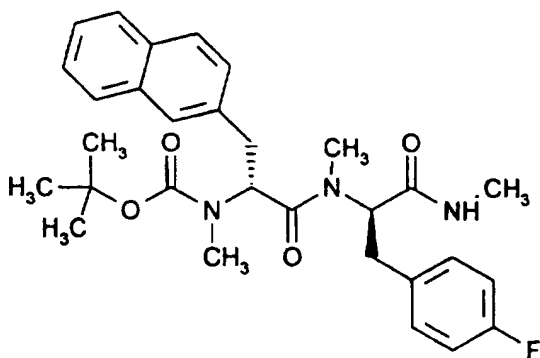
Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 30
 5 min at room temperature. Methylene chloride (30 mL), an aqueous solution of
 sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen
 carbonate (solid), were added to the reaction mixture, until pH 9. The organic phase
 was dried (magnesium sulfate) and evaporated *in vacuo* to afford 0.62 g of (2R)-3-
 (4-fluorophenyl)-N-methyl-2-methylaminopropionamide.

10

¹H-NMR (CDCl₃) δ : 1.31 (s, 1H); 2.29 (s, 3H); 2.65-2.73 (m, 1H); 2.82 (d, 3H); 3.12-
 3.20 (m, 2H); 6.96-7.02 (m, 2H); 7.11 (s, 1H); 7.14-7.20 (m, 2H).

((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-

15 naphthyl)-ethyl)methylcarbamic acid tert-butylester:



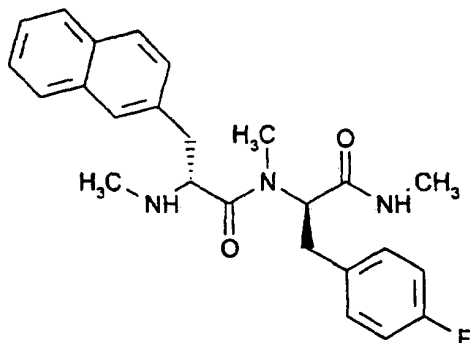
20 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (1.0 g; 3.1
 mmol) was dissolved in methylene chloride (20 mL). 1-Hydroxy-7-azabenzotriazole
 (0.43 g; 3.1 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide

hydrochloride (0.63 g; 3.3 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

(2R)-3-(4-Fluorophenyl)-N-methyl-2-(methylamino)propionamide (0.6 g; 2.9 mmol) and diisopropylethylamine (0.54 mL; 3.1 mmol) was added and the reaction mixture
 5 was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was added and the reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed *in vacuo* and the residue was
 10 chromatographed on silica (4.0 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.07 g of ((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.34 (s, 9H); 2.23 (d, 3H);
 15 2.76 (s, 3H); 2.87 (s, 3H); 5.70 (dd, 1H); 5.95 (dd, 1H).

(2R)-N-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide:



20

((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamic acid tert-butylester. (1.0 g; 1.92 mmol) was dissolved in methylene chloride (5 mL). Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 15 min at room temperature. Methylene chloride
 25 (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH

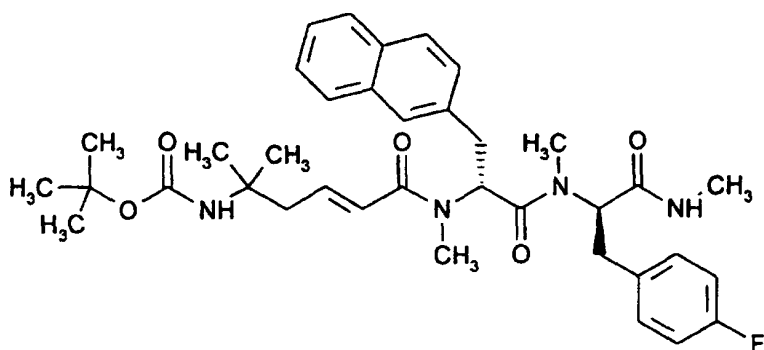
9; 25 mL) and sodium hydrogen carbonate (solid) was added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.75 g of (2R)-N-((1R)-2-(4-fluorophenyl)-1-methylcarbamoyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

5

¹H-NMR (CDCl₃) δ : 1.81 (s, 3H); 2.07 (d, 3H); 2.54 (s, 3H); 2.68-2.77 (m, 1H); 2.88-2.97 (m, 1H); 3.18 (dd, 1H); 3.27 (dd, 1H); 3.8 (dd, 1H); 4.95 (s, 1H); 5.43 (dd, 1H); 6.72 (t, 1H); 6.90 (t, 2H); 7.12 (dd, 2H); 7.32 (d, 1H); 7.42-7.50 (m, 2H); 7.62 (s, 1H); 7.70-7.83 (m, 2H).

10

(4(((1R)-1(((1R)-2(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:



15

(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.22 g; 0.89 mmol, prepared as in example 1) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-

20 ethylcarbodiimide hydrochloride (0.2 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

(2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture was stirred for 12 hours

25 at room temperature.

Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.34 g of (4-(((1R)-1-(((1R)-2-(4-fluorophenyl)-1-methylcarbamoyl-ethyl)methylcarbamoyl)-2-(2-naphthyl)-ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.

10 ¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 0.85 (s, 3H); 0.87 (s, 3H); 1.42 (s, 9H); 2.12 (d, 3H); 2.72 (s, 3H); 2.96 (s, 3H); 5.75 (dd, 1H); 5.92 (dd, 1H); 6.12 (dd, 1H).

(4-(((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-methylcarbamoyl-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester (0.33 g; 0.51 mmol) was dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.18 g of the title compound.

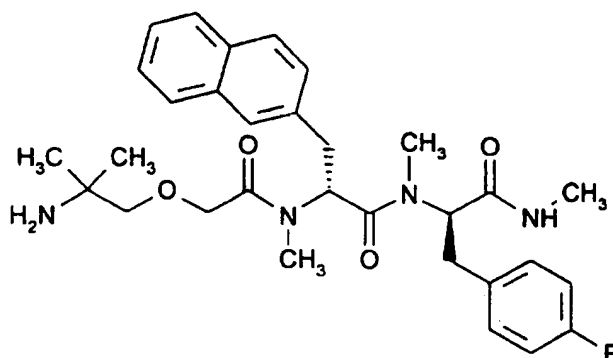
25 ¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 1.15 (s, 6H); 2.14 (d, 3H); 2.73 (s, 3H); 3.09 (s, 3H); 5.23 (dd, 1H); 5.90 (dd, 1H); 6.12 (dd, 1H).

PDMS: m/z 547.4 (M+H)⁺

HPLC: R_t = 32.05 min (Method A1)

Example 14

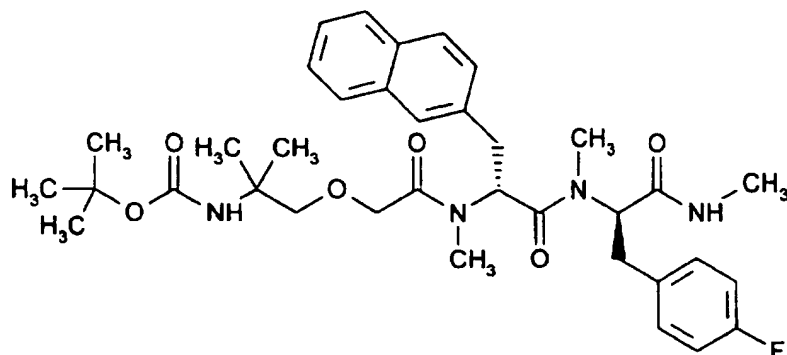
(2R)-2-(((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide:



5

(2-(((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-methyl-carbamoyl)ethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-methylcarbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid

10 tert-butylester:



(2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.22 g; 0.89 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.20 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture

15

was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and water (50 mL) and
5 dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.53 g of (2-((((1R)-1-(((1R)-2-(4-fluorophenyl)-1-methylcarbamoyl)ethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamoyl)-methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester.

10 ¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 1.20 (s, 3H); 1.25 (s, 3H); 1.44 (s, 9H); 2.18 (d, 2H); 2.59 (s, 3H); 2.74 (s, 3H); 2.77 (d, 3H); 4.02 (s, 2H); 5.25 (dd, 1H); 5.82 (dd, 1H).

(2-((((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-
15 2-(2-naphthyl)ethyl)-methylcarbamoyl)-methoxy)-1,1-dimethylethyl)carbamic acid tert-butylester (0.53 g; 0.81 mmol) was dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen
20 carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.26 g of the title compound.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ 0.99 (s, 3H); 1.09 (s, 3H);
25 2.25 (d, 3H); 2.28 (s, 3H); 2.95 (s, 3H); 3.90 (s, 2H); 5.31 (dd, 1H); 5.83 (dd, 1H).

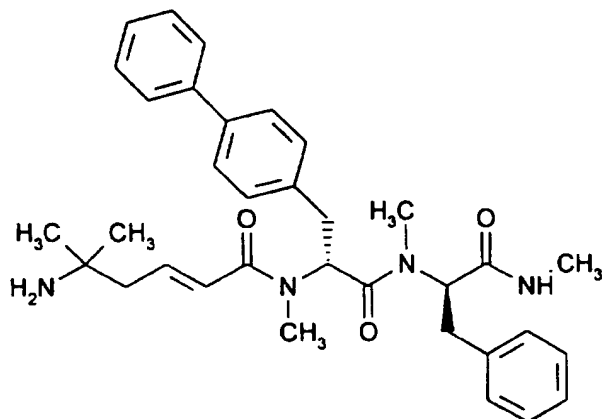
PDMS: m/z 550.6 (M+H)⁺

HPLC: t_r = 31.83 min (A1)

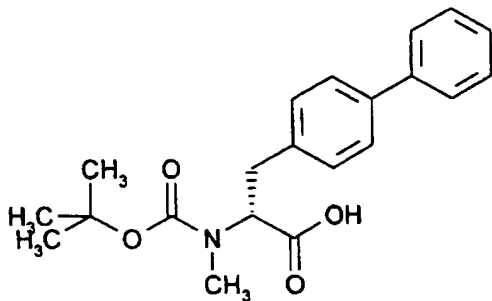
Example 15

(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-2-(biphenyl-4-yl)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)methylamide:

5



(2R)-3-(1,1'-Biphenyl-4-yl)-2-(N-tert-butoxycarbonyl-N-methylamino)propionic acid:



10

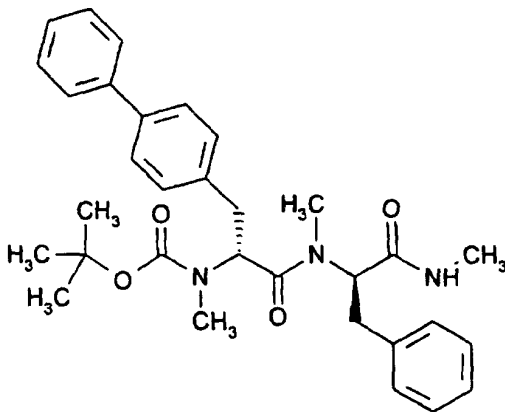
3-(1,1'-Biphenyl-4-yl)-2-tert-butoxycarbonylaminopropionic acid (5.0 g; 14.66 mmol) was dissolved in dry tetrahydrofuran (45 mL). Iodomethane (7.3 mL; 117.3 mmol) was added and the reaction mixture was cooled to 0°C. Sodium hydride (1.75 g; 15 44.0 mmol) was added and the reaction mixture was stirred for 5 days at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise. The solvent was removed in vacuo and the residue was dissolved in an aqueous solution of sodium hydrogen carbonate (saturated; 50 mL) and washed with diethyl ether (30 mL). The aqueous phase was acidified to pH 3 using citric

acid (5 %) and extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with an aqueous solution of sodium thiosulfate (5 %; 75 mL) and dried (magnesium sulfate). The solvent was removed *in vacuo* to afford 3.85 g of (2R)-3-(1,1'-biphenyl-4-yl)-2-(N-tert-butoxycarbonyl-N-methylamino)propionic acid.

5

¹H NMR (200 MHz, CDCl₃) δ (mixture of rotamers) 1.47 (s, 4.5H), 1.49 (s, 4.5H), 2.54 (s, 1.5H), 2.56 (s, 1.5H), 3.00-3.40 (bm, 1H), 3.45-3.91 (bm, 1H), 4.53-4.55 (m, 0.5H), 4.55-4.58 (m, 0.5H), 7.3-7.6 (m, 9H).

- 10 ((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)ethyl)methylcarbamic acid tert-butylester:



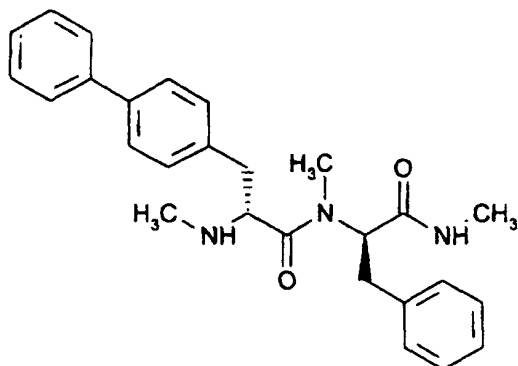
- (2R)-3-(1,1'-Biphenyl-4-yl)-2-(N-tert-butoxycarbonyl-N-methylamino)propionic acid (1.50 g; 4.23 mmol) was dissolved in methylene chloride (20 mL). 1-Hydroxy-7-azabenzotriazole (0.57 g; 4.23 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.89 g; 4.65 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.
- N-Methyl-2-methylamino-3-phenylpropionamide (0.81 g; 4.23 mmol) and diisopropylethylamine (0.73 mL; 4.23 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen carbonate (sat; 50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and water (50 mL) and dried (magnesium sulfate).

The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 25 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.02 g of ((1R)-2-(1,1'-biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methylcarbamic acid tert-butyl ester.

5

¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 1.15 (s, 6H); 1.31 and 1.34 (two s; 9H); 2.24 (d, 3H); 2.80 (s, 3H); 2.98 (s, 3H); 4.98 (m, 1H); 5.38 (m, 1H).

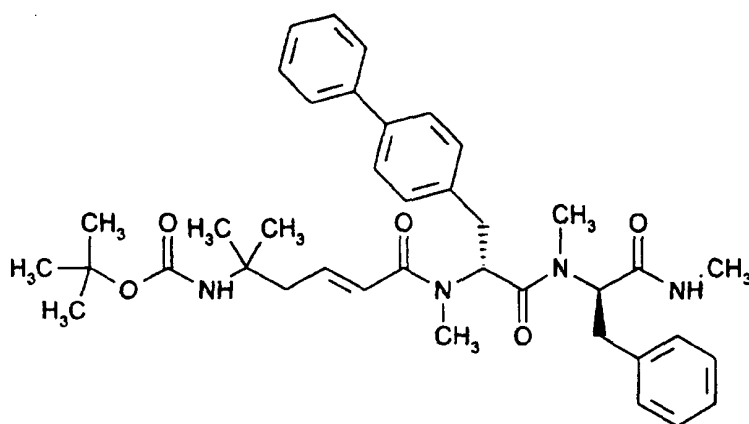
3-(1,1'-Biphenyl-4-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide:



((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)ethyl)methyl-carbamic acid tert-butylester (1.0 g; 1.8 mmol) was dissolved in methylene chloride (4 mL). Trifluoroacetic acid (4 mL) was added and the reaction mixture was stirred for 15 min at room temperature. Methylene chloride (40 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 40 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and the solvent was removed in vacuo to afford 0.76 g of (2R)-3-(1,1'-biphenyl-4-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 1.71 (s, 3H); 2.58 (s, 3H); 2.69 (d, 3H); 5.52 (dd, 2H).

((3E)-4-(((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:



5

(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.24 g; 0.98 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
 10 (0.2 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-3-(1,1'-Biphenyl-4-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was
 15 added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 20 cm) using ethyl acetate/heptane (2:1) as eluent
 20 to afford 0.46 g of ((3E)-4-(((1R)-2-(1,1'-biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)-carbamic acid tert-butylester.

¹H-NMR (CDCl₃) (selected peaks for major rotamer): 1.22 (s, 3H); 1.23 (s, 3H);

1.42 (s, 9H); 2.75 (d, 3H); 2.82 (s, 3H); 2.98 (s, 3H); 5.54 (dd, 1H); 5.82 (dd, 1H); 6.12 (d, J=17Hz, 1H).

((3E)-4-(((1R)-2-(1,1'-Biphenyl-4-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester (0.45 g; 0.69 mmol) was dissolved in methylene chloride (10 mL). Trifluoroacetic acid (10 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.22 g of the title compound.

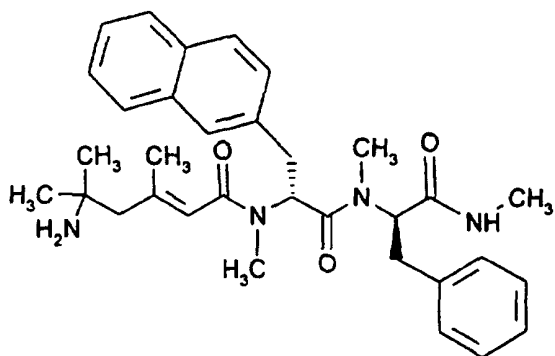
¹H-NMR (CDCl₃) (selected peaks for major rotamer) d : 1.18 (s, 6H); 2.75 (d, 3H); 2.78 (s, 3H); 2.97 (s, 3H); 5.45 (dd, 1H); 5.75 (dd, 1H); 6.08 (d, J=17Hz, 1H).

ESMS: m/z 555.8 (M+H)⁺

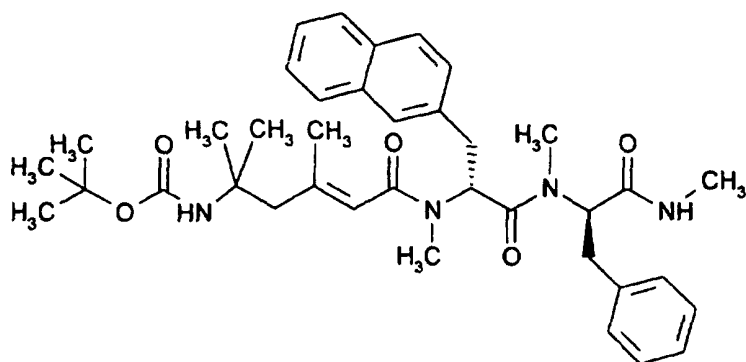
HPLC: R_t = 34.45 min (Method A1).

Example 16

(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



((3E)-1,1,3-Trimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-methyl carbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid
 5 tert butylester:



- 10 (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid (0.30 g ; 1.17 mmol.) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazol (0.16 g ; 1.17 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g ; 1.28 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.
- 15 N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (0.47 g ; 1.67 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.20 mL; 1.66 mmol) was added and the reaction was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added and the reaction was washed with water (10 mL) , an aqueous

solution of sodium hydrogen sulfate (10% ; 10 mL) and an aqueous solution of sodium hydrogen carbonate (pH 8 ; 10 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.37 g of

5 ((3E)-1,1,3-trimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester.

10 ¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 1.16 (s, 3H); 1.17 (s, 3H); 1.42 (s, 9H); 1.68 (s, 3H); 2.75 (d, 3H); 2.76 (s, 3H); 2.95 (s, 3H); 5.21 (dd, 1H); 5.51 (s, 1H); 5.59 (dd, 1H).

((3E)-1,1,3-Trimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid

15 tert butylester (0.37 g ; 0.56 mmol) was dissolved in methylene chloride (2 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (2 mL), water (5mL) and sodium hydrogen carbonate (solid) were added to the reaction until pH = 9. The aqueous phase was

20 extracted with methylene chloride (3 x 10 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.17 g of the title compound.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ : 1.18 (s, 3H); 1.19 (s, 3H);

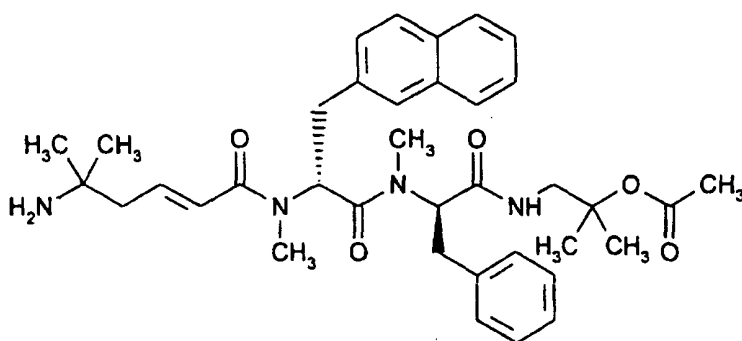
25 1.67 (s, 3H); 2.75 (d, 3H); 2.76 (s, 3H); 2.95 (s, 3H); 5.52 (dd, 1H); 5.62 (s, 1H); 5.86 (dd, 1H).

HPLC : R_t = 31.78 min (Method A1)

30 PDMS : m/z 542.8 (M+H)⁺

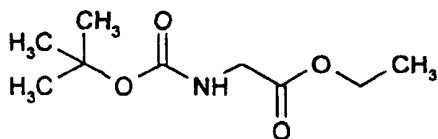
Example 17

- 5 2-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:



10

Ethyl 2-(tert-butoxycarbonylamino)acetate



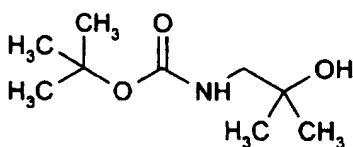
15

- (tert-Butoxycarbonylamino)acetic acid (4.00 g, 22.8 mmol) was dissolved in dichloromethane (8 ml). Ethanol (1.60 ml, 27.40 mmol) and 4-
- 20 dimethylaminopyridine (0.31 g, 25.1 mmol) were added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (4.81 g, 25.11 mmol) was added. The solution was stirred for 16 h, while warming up to room temperature. It was diluted with ethyl acetate (150 ml) and 10% aqueous sodium hydrogen sulfate solution (100 ml). The phases were separated. The aqueous

phase was extracted with ethyl acetate (4 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (150 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (100 g), using ethyl acetate/heptane (1:4) as eluent, to give 4.25 g of ethyl 2-(tert-butoxycarbonylamino)acetate.

¹H-NMR (CDCl₃): d 1.30 (t, 3 H); 1.47 (s, 9 H); 3.90 (d, 2 H); 4.21 (q, 2 H); 5.06 (br, 1 H).

2-Hydroxy-2-methylpropylcarbamic acid tert-butyl ester

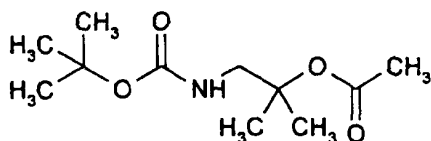


Ethyl 2-(tert-butoxycarbonylamino)acetate (4.17 g, 20.52 mmol) was dissolved in tetrahydrofuran (60 ml). The solution was cooled to -78 °C. A 22% solution of methyl magnesium chloride in toluene/tetrahydrofuran (purchased from Chemmetallgesellschaft, 27.1 ml, 67.72 mmol) was added dropwise. The reaction mixture was stirred for 1.5 h at -78 °C and then warmed to room temperature. A 10% aqueous solution of ammonium chloride (200 ml) was added dropwise. The phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (110 g), using ethyl acetate/heptane (1:1) as eluent, to give 1.31 g of 2-hydroxy-2-methylpropylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): d 1.21 (s, 6 H); 1.45 (s, 9 H); 1.34 (d, 2 H); 5.00 (br, 1 H).

2-(tert-Butoxycarbonylamino)-1,1-dimethylethyl acetate

5



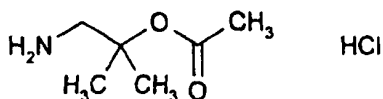
2-Hydroxy-2-methylpropylcarbamic acid tert-butylester (510 mg, 2.69 mmol) was dissolved in dichloromethane (7 ml). The solution was cooled to 0 °C.

- 10 Ethyldiisopropylamine (0.70 ml, 4.04 mmol), 4-dimethylaminopyridine (33 mg, 0.27 mmol), and acetic acid anhydride (0.33 ml, 3.50 mmol) were added successively. The reaction mixture was stirred for 16 h, while slowly warming up to room temperature. It was diluted with ethyl acetate (30 ml) and extracted with 1N hydrochloric acid (30 ml). The aqueous phase was extracted with ethyl acetate (2 x
- 15 20 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (50 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (100 g), using ethyl acetate/heptane (1:2) as eluent, to give 550 mg of 2-(tert-butoxycarbonylamino)-1,1-dimethylethyl acetate.

20

¹H-NMR (CDCl₃): δ 1.45 (s, 9 H); 1.46 (s, 6 H); 2.00 (s, 3 H); 3.35 (d, 2 H); 4.96 (br, 1 H).

25 2-Amino-1,1-dimethylethyl acetate hydrochloride

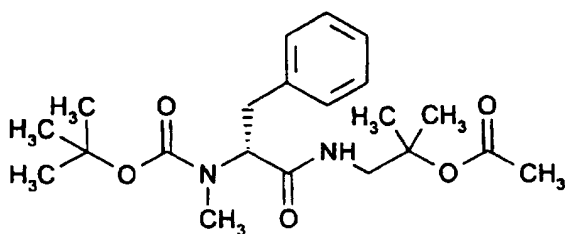


2-(tert-Butoxycarbonylamino)-1,1-dimethylethyl acetate (508 mg, 2.2 mmol) was dissolved in ethyl acetate (6 ml). 3 M hydrogen chloride in ethyl acetate (4 ml, 12 mmol) was added. The reaction mixture was stirred for 20 h at room temperature.
5 The precipitation was filtered off and washed with diethyl ether (50 ml). It was dried in vacuo to give 246 mg of 2-amino-1,1-dimethylethyl acetate hydrochloride.

¹H-NMR (DMSO d₆): d 1.45 (s, 6 H); 2.00 (s, 3 H); 3.09 (s, 2 H); 8.25 (br, 3 H).

10

2-((2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate



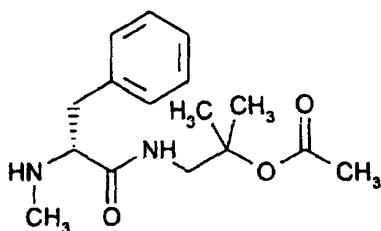
15

(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-phenylpropionic acid (391 mg, 1.4 mmol) was dissolved in N,N-dimethylformamide (6 ml). 1-Hydroxybenzotriazole
20 hydrate (189 mg, 1.4 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride were added. The reaction mixture was stirred for 10 min at room temperature. 2-Amino-1,1-dimethylethyl acetate hydrochloride (237 mg, 1.4 mmol) was added as a solid. Ethyldiisopropylamine (0.53 ml, 3.1 mmol) was added. The reaction mixture was stirred for 20 h at room temperature. It was diluted with ethyl
25 acetate (200 ml) and washed with 1N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was

purified by flash chromatography on silica (80 g), using ethyl acetate/heptane (1:1) as eluent, to give 442 mg of 2-((2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate.

5 ¹H-NMR (CDCl₃): d 1.30 and 1.35 (both s, together 6 H); 1.41 (s, 9 H); 1.98 (s, 3 H); 2.70 - 3.05 (m, 4 H); 3.30 - 3.65 (m, 3 H); 4.75 - 4.95 (m, 1 H); 6.65 (br, 1 H); 7.15 - 7.35 (m, 5 H).

10 1,1-Dimethyl-2-((2R)-2-methylamino-3-phenylpropionylamino)-ethyl acetate:

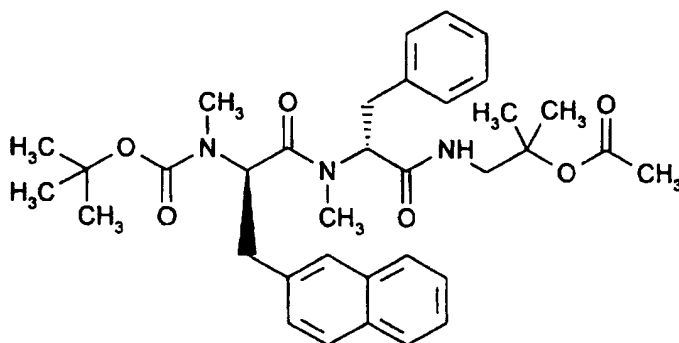


15 2-((2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate (426 mg, 1.1 mmol) was dissolved in dichloromethane (2 ml) and cooled to 0 °C. Trifluoroacetic acid (2 ml) was added and the reaction mixture was stirred for 15 min at 0°C. The solvent was removed in vacuo at 20°C. The residue was dissolved in dichloromethane (50 ml) and the solvent was removed in
20 vacuo. This latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (45 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 312 mg of 1,1-dimethyl-2-((2R)-2-methylamino-3-phenylpropionylamino)ethyl acetate.

25

¹H-NMR (CDCl₃): d 1.43 (s, 6 H); 2.00 (s, 3 H); 2.30 (s, 3 H); 2.67 (dd, 1 H); 3.24 (m, 2 H); 3.53 (ABX, 2 H); 7.15 - 7.45 (m, 5 H); 7.61 (br, 1 H).

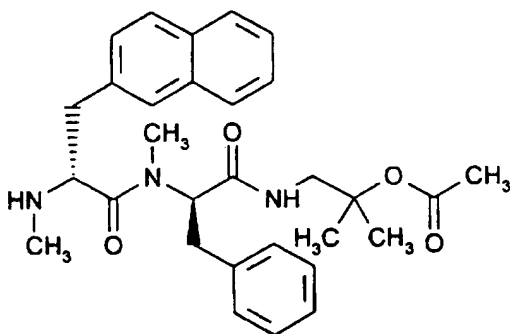
2-((2R)-2-(N-((2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-naphthyl)-
 5 propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:



(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (373
 mg, 1.13 mmol) was dissolved in N,N-dimethylformamide (2 ml) and
 10 dichloromethane (2 ml). 1-Hydroxy-7-azabenzotriazole (153 mg, 1.13 mmol) was
 added. The solution was cooled to 0°C. N-(3-Dimethylaminopropyl)-N'-ethyl-
 carbodiimide hydrochloride (217 mg, 1.13 mmol) was added. The reaction mixture
 was stirred for 10 min at 0 °C. 1,1-Dimethyl-2-((2R)-2-methylamino-3-
 phenylpropionylamino)-ethyl acetate (301 mg, 1.03 mmol) was dissolved in
 15 dichloromethane (2 ml) and added. Ethyldiisopropylamine (0.18 ml, 1.03 mmol) was
 added. The reaction mixture was stirred for 20 h, while it was warming up to room
 temperature. It was diluted with ethyl acetate (100 ml) and washed with 1 N
 hydrochloric acid. The aqueous phase was extracted with ethyl acetate (3 x 30 ml).
 The combined organic layers were washed with saturated sodium hydrogen
 20 carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was
 removed in vacuo. The crude product was purified by flash chromatography on
 silica (85 g), using ethyl acetate/heptane (1:1) as eluent, to give 547 mg of 2-((2R)-
 2-(N-((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(2-naphthyl)propionyl)-N-
 methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate.

¹H-NMR (CDCl₃, selected values): d 0.98 and 1.23 (both s, together 9 H); 1.95 and 2.03 (both s, together 3 H); 2.18 and 2.25 (both s, together 3 H); 5.05 and 5.35 - 5.55 (both m, together 2 H).

- 5 1,1-Dimethyl-2-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropionylamino)ethyl acetate:



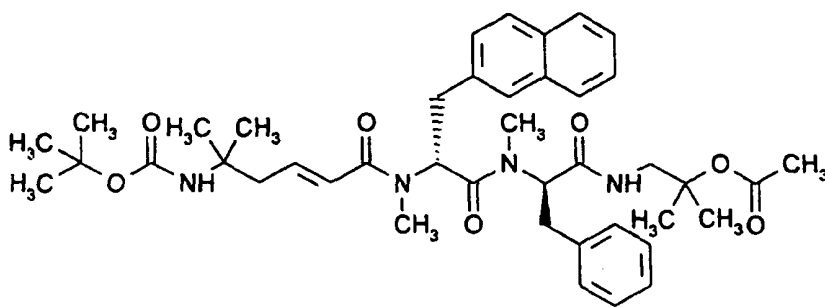
- 2-((2R)-2-(N-((2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-naphthyl)-
 10 propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate (511 mg, 0.85 mmol) was dissolved in dichloromethane (2 ml) and cooled to 0 °C. Trifluoroacetic acid (2 ml) was added, and the solution was stirred for 15 min at 0°C. The solvents were removed in vacuo without warming. The residue was dissolved in dichloromethane (50 ml), and the solvent was removed in vacuo. The latter
 15 procedure was repeated two times. The crude product was purified by flash chromatography on silica (30 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 160 mg of 1,1-dimethyl-2-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropionylamino)ethyl acetate.

20

¹H-NMR (CDCl₃, selected values): d 0.82 and 0.90 (s and m, together 6 H); 1.86 and 1.91 (both s, together 3 H); 2.01 and 2.35 (both s, together 3 H); 2.75 and 2.95 (both s, together 3 H); 4.60 and 5.50 (both dd, together 1 H).

25

2-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate:



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(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (81 mg, 0.33 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). 1-Hydroxy-7-azabenzotriazole (45 mg, 0.33 mmol) was added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (69 mg, 0.36 mmol) was added. A solution of 1,1-dimethyl-2-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropionylamino)ethyl acetate (152 mg, 0.30 mmol) in dichloromethane (2 ml) and ethyldiisopropylamine (0.05 ml, 0.30 mmol) were added successively. The solution was stirred for 16 h, while warming up to room temperature. It was diluted with ethyl acetate (150 ml), washed with 1 N hydrochloric acid (100 ml) and saturated sodium hydrogen carbonate solution, and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (40 g), using ethyl acetate/heptane (first 1:1 (250 ml), then 2:1) to give 221 mg of 2-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate.

¹H-NMR (CDCl₃, selected values): d 5.25, 5.45, 5.60, and 5.90 (all dd, together 2 H); 5.92 - 6.07 (m, 1 H); 6.60 - 6.85 (m, 1 H).

25

2-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl acetate (199 mg, 0.27 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (2 ml) was added. The solution was stirred for 15 min at 0 °C. The solvent was removed in vacuo at 20 °C. The residue was dissolved in dichloromethane (50 ml) and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (25 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 75 mg of the title compound.

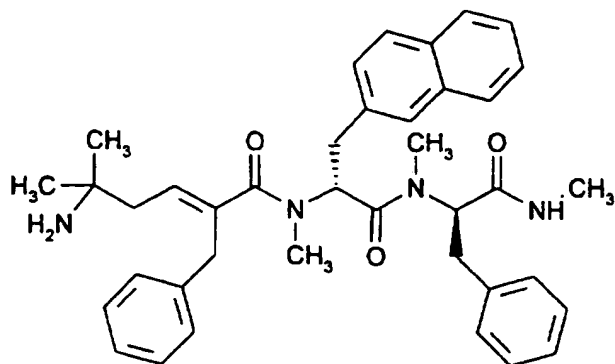
¹H-NMR (CDCl₃, selected values): d 0.95, 0.96, 0.98, 0.99, 1.16, 1.20, 1.35, and 1.40 (all s, together 12 H); 1.90 and 1.95 (both s, together 3 H); 2.83 and 2.84 (both s, together 3 H); 2.98 and 3.03 (both s, together 3 H); 5.25, 5.45, 5.57, and 5.90 (all dd, together 2 H); 6.95 - 6.10 (m, 1 H); 6.65 - 6.90 (m, 1 H).

HPLC: (A1) R_t = 36.15 min.

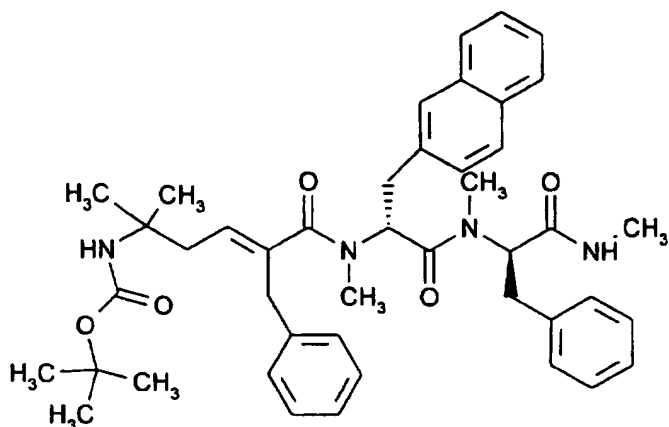
MS: 630±1 [M+1]⁺

Example 18

(2E)-5-Amino-2-benzyl-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



(2E)-2-Benzyl-5-(tert butoxycarbonylamino)-5-methylhex-2-enoic acid methyl-(1-
 5 (methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl amide:



(2E)-2-Benzyl-5-tert-butoxycarbonylamino-5-methylhex-2-enoic acid (0.125 g ; 0.38
 10 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole
 (0.05 g; 0.37 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide
 hydrochloride (0.08 g; 0.41 mmol) were added and the reaction mixture was stirred
 for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-
 methylcarbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (0.151 g; 0.37 mmol)
 15 was dissolved in methylene chloride (5 mL) and added. Diisopropylethylamine
 (0.064 mL; 0.37 mmol) was added. The reaction mixture was stirred for 12 hours at
 room temperature. Methylene chloride (5 mL) was added. The reaction mixture was
 washed with water (10 mL), an aqueous solution of sodium hydrogen sulfate (10%;

10 mL), and an aqueous solution of sodium hydrogen carbonate (pH 8; 10 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2 x 20 cm) using ethylacetat/methylene chloride 1:1 as eluent to afford 0.08 g of (2E)-2-Benzyl-5-(tert-butoxy-carbonylamino)-5-methylhex-
5 2-enoic acidmethyl-(1-(methyl-(1-methylcarbamoyl-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl amide.

¹H-NMR: (CDCl₃)(selected peaks for major rotamer) d 0.96 (s, 3H); 1.11 (s, 3H); 1.38 (s, 9H); 2.65 (d, 3H); 2.71 (s, 3H); 2.99 (s, 3H); 4.80 (m, 1H); 5.30 (m, 3H);
10 5.80 (t, 1H).

(2E)-2-Benzyl-5-(tert butoxycarbonylamino)-5-methylhex-2-enoic acid methyl-(1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl amide (0.10 g ; 0.14 mmol) was dissolved in methylene chloride (2 mL) and trifluoroacetic
15 acid (1 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (3 mL) and sodium hydrogen carbonate (solid) were added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 10 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.09 g of the title compound.

20 ¹H - NMR: (CDCl₃) (selected peaks for major rotamer) d 0.89 (s, 3H); 0.92 (s, 3H); 2.38 (d, 3H); 2.45 (s, 3H); 2.95 (s, 3H); 5.21 (m, 1H); 5.45 (m, 1H).

ESMS : m/z 618.2 (M+H)⁺

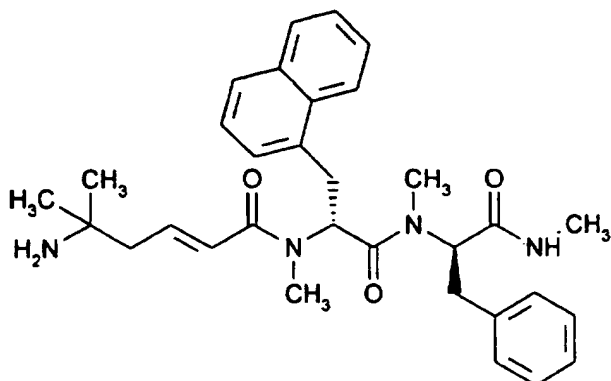
25

HPLC : R_t = 37.53 min (Method A1)

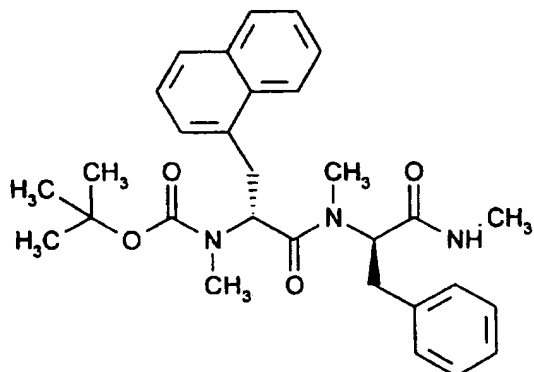
Example 19

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(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(1-naphthyl)ethyl)amide:



- 5 Methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamate tert-butylester:



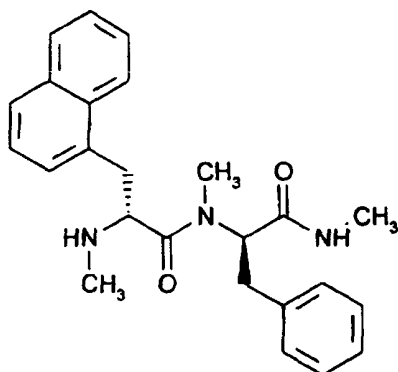
- 10 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-(1-naphthyl)- propionic acid (2.00 g ; 6.07 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.83 g ; 6.07 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.28 g ; 6.68 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-3-phenyl-propionamide (1.17 g ; 6.07 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (1.04 mL; 6.07 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (20 mL) was added. The reaction mixture was washed with water (20 mL), an

aqueous solution of sodium hydrogen sulfate (10 %; 20 mL), and an aqueous solution of sodium hydrogen carbonate (saturated 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethyl acetat/methylene chloride 1:1 as eluent to afford
 5 0.77 g of methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamamic acid tert-butylester.

¹H-NMR : (CDCl₃) (selected peaks for major rotamer) δ 1.39 (s, 9H); 2.30 (s, 3H); 2.75 (s, 3H); 3.68 (dd, 1H); 5.35 (dd, 1H).

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(2R)-N-Methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide:



15

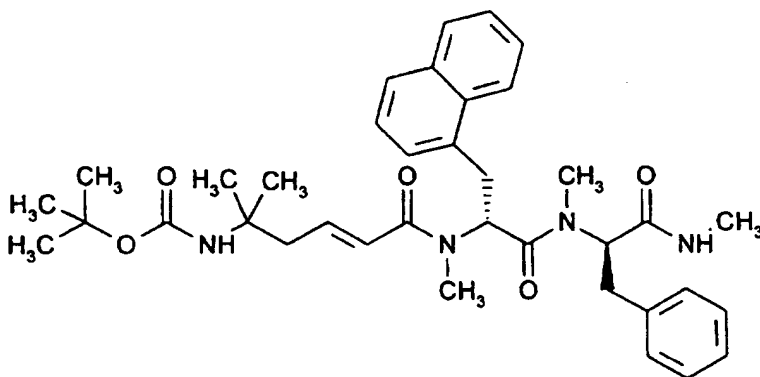
Methyl-((1R)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamamic acid tert butyl ester (0.77 g; 1.52 mmol) was dissolved in methylene chloride (4 mL) and trifluoroacetic acid (4 mL) was added. The reaction
 20 mixture was stirred for 30 min at room temperature. Water (5 mL) and methylene chloride (5 mL) were added. An aqueous solution of sodium hydrogen carbonate was added until pH 8. The organic phase was extracted with methylene chloride (3 x 10 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.64 g of (2R)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide.
 25

¹H-NMR : (CDCl₃)(selected peaks for major rotamer) δ 1.69 (s, 3H); 2.05 (s, 3H); 2.57 (d, 3H); 3.91 (dd, 1H); 5.45 (dd, 1H).

5

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester:

10



(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (0.19 g ; 0.80 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.108 g; 0.795 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.87 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide (0.32 g; 0.80 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.14 mL; 0.80 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (5 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethylacetate/methylene chloride 1:1 as

25

eluent to afford 0.26 g of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester.

5 ¹H-NMR : (CDCl₃)(selected peaks for major rotamer) δ 1.31 (s, 3H); 1.32 (s, 3H); 1.48 (s, 9H); 2.45 (d, 3H); 2.65 (s, 3H); 2.92 (s, 3H); 5.22 (dd, 1H); 6.03 (dd, 1H); 6.14 (d, 1H).

10 ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester (0.25 g; 0.40 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (5 mL) and solid sodium hydrogen carbonate
15 were added until pH 8. The reaction mixture was washed with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo to afford 0.21 g of the title compound.

¹H-NMR : (CDCl₃) (selected peaks for major rotamer) δ 1.22 (s, 3H); 1.23 (s, 3H);
20 2.82 (d, 3H); 2.92 (s, 3H); 3.08 (s, 3H); 5.22 (dd, 1H); 5.92 (dd, 1H); 6.12 (d, 1H).

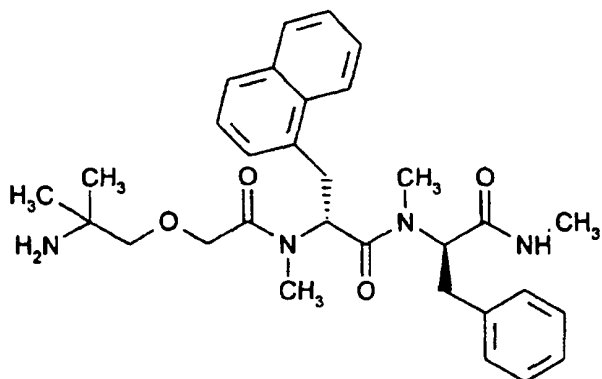
ESMS : m/z 529.2 (M+H)⁺

HPLC : R_t = 30.90 min (Method A1)

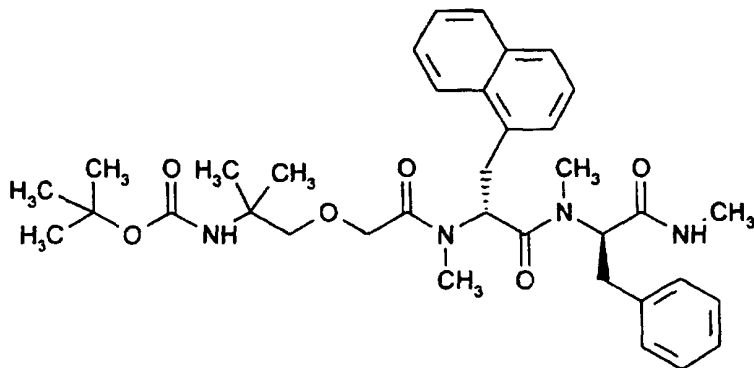
25

Example 20

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide:
30



- 5 (1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert butylester:



- 10 (2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.14 g; 0.54 mmol)(prepared as in example 33) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.07 g; 0.54 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl) propionamide (0.21 ; 0.54 mmol)
- 15 was dissolved in methylene chloride (10 mL) and added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of

sodium hydrogen sulfate (10%; 20 mL) and an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2 x 20 cm) using methylene chloride/ethyl acetate (1:1) as eluent to afford 0.27 g of (1,1-
5 dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.39 (s, 3H); 1.40 (s, 3H);
10 1.45 (s, 9H); 2.52 (s, 3H); 2.71 (d, 3H); 2.98 (s, 3H); 5.27 (dd, 1H); 5.95 (dd, 1H).

(1,1-Dimethyl-2-((N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(1-naphthyl)-ethyl)carbamoyl)methoxy)ethyl)carbamic acid tert-butylester (0.26 g; 0.41 mmol) was dissolved in methylene chloride (3 mL)
15 and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Methylene chloride (5 mL), an aqueous solution of sodium hydrogen carbonate (saturated) and sodium hydrogen carbonate (solid) were added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 15 mL) and the combined organic layers were dried (magnesium sulfate). The
20 solvent was removed in vacuo to afford 0.25 g of the title compound.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.18 (s, 3H); 1.23 (s, 3H);
2.48 (s, 3H); 2.53 (s, 3H); 2.99 (s, 3H); 4.54 (dd, 1H); 5.25 (dd, 1H).

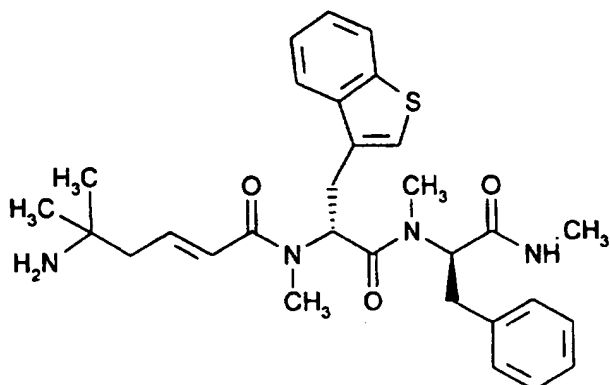
25 ESMS : m/z 533.2 (M+H)⁺

HPLC : R_t = 30.68 min (Method A1)

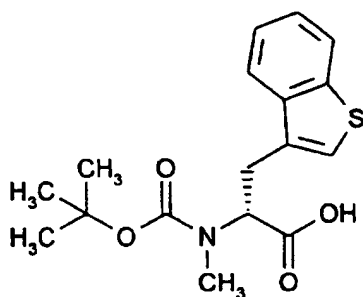
Example 21

30

(2E)-5-Amino-5-methylhex-2-enoic acid-((1R)-2-(benzo[b]thiophen-3-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methanamide:



(2R)-3-(Benzo[b]thiophen-3-yl)-2-(tert-butoxycarbonylmethylamino)propionic acid:



5

(2R)-3-(Benzo[b]thiophen-3-yl)-2-tert-butoxycarbonylamino-propionic acid (2.65 g; 8.25 mmol) was dissolved in dry tetrahydrofuran. Methyl iodide was added and the reaction mixture was cooled to 0 °C. Sodium hydride (60 % in mineral oil, 0.80 g, 24.8 mmol) was added. The reaction mixture was stirred for 48 hours at room temperature. Ethyl acetate (25 mL) and water (10 mL) were added dropwise. The solvent was removed in vacuo and the residue was dissolved in ether (15 mL) and water (15 mL). The organic phase was washed with an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL). To the aqueous phase was added citric acid (5 %) until pH 3 and extracted with ethyl acetate (4 x 20 mL). The combined organic phases were washed with water (2 x 30 mL), an aqueous solution of sodium thiosulfate (5 %; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was dissolved in ether (10 mL). Dicyclohexylamine (5 mL) was added. The precipitated crystals were filtered off, washed with ether (2 x 10 mL) and dissolved in water (30 mL). An aqueous solution of sodium hydrogen sulfate (10 %; 20 mL) and ethyl acetate (40 mL) were added.

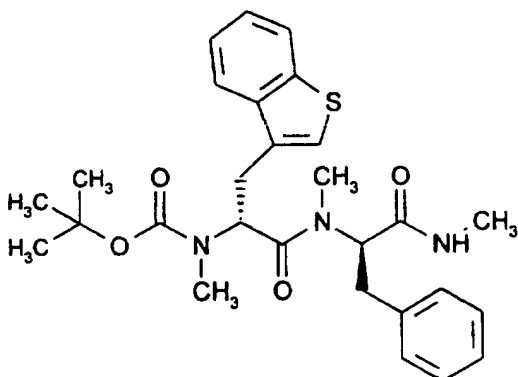
20

The aqueous phase was extrated with ethylacetate (4 x 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 3.75 g of (2R)-3-(benzo[b]thiophen-3-yl)-2-(tert-butoxycarbonyl methylamino)propionic acid.

- 5 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.45 (s, 9H); 2.81 (s, 3H); 3.21-3.61 (m, 2H); 4.88 (dd, 1H); 7.18 (s, 1H).

((1R)-2-(Benzo[b]thiophen-3-yl)-(methyl-((1R)-1-methylcarbamoyl-2-phenyl-ethyl)carbamoyl)ethyl)methylcarbamic acid tert butylester:

10



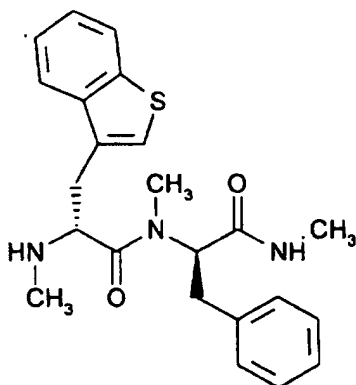
- (2R)-3-(Benzo[b]thiophen-3-yl)-2-(tert-butoxycarbonyl- methylamino)propionic acid
- 15 (2.00 g ; 5.96 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.81 g; 5.96 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.26 g ; 6.56 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-
- N-Methyl-2-methylamino-3-phenylpropionamide (1.15 g; 5.96 mmol) was dissolved
- 20 in methylene chloride (10 mL) and added. Diisopropylethylamine (1.02 mL; 5.96 mmol) were added. The reaction mixture was stirred for 48 hours. Methylene chloride (10 mL) was added. The reaction was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 30 mL) and dried (magnesium sulfate).
- 25 The solvent was removed in vacuo and the residue was chromatographed on silica

(3 x 30 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.89 g of ((1R)-2-(benzo[b]thiophen-3-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl carbamic acid tert-butylester.

- 5 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.43 (s, 9H); 2.26 (d, 3H); 2.75 (s, 3H); 2.76 (s, 3H); 4.96 (dd, 1H); 5.05 (dd, 1H).

(2R)-3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide:

10



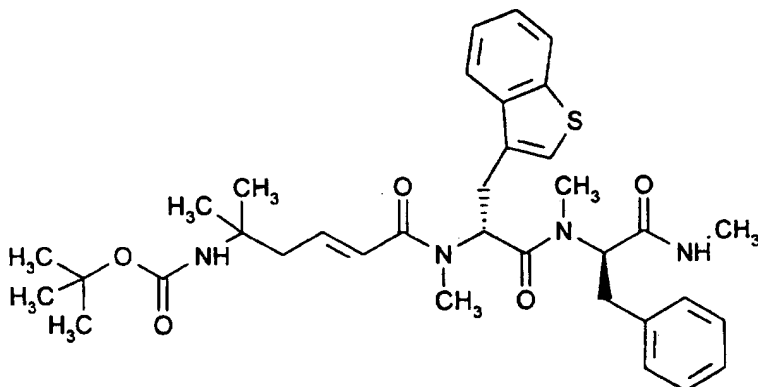
((1R)-2-(Benzo[b]thiophen-3-yl)-1-(methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methylcarbamic acid tert-butylester (0.89 g; 1.70 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added.

- 15 The reaction mixture was stirred for 45 min at room temperature. Water (5 mL) was added. Methylene chloride (5 mL), an aqueous solution of sodium hydrogen carbonate (saturated) and sodium hydrogen carbonate (solid) was added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo
- 20 to afford 0.66 g of (2R)-3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.71 (s, 3H); 2.38 (s, 3H); 2.62 (d, 3H); 3.82 (dd, 1H); 5.47 (dd, 1H).

((3E)-4-(((1R)-2-(Benzo[b]thiophen-3-yl)-1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:

5



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.19 g; 0.78 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.11 g; 0.78 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (0.16 g; 0.86 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.

3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide (0.32 g; 0.78 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.13 mL; 0.78 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature.

Methylene chloride (10 mL) was added. The reaction was washed with water (20 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 20 mL), an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (2 x 20 cm) using ethylacetate/methylene chloride (1:1) as eluent to afford 0.26 g of ((3E)-4-(((1R)-2-(benzo[b]thiophen-3-yl)-1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 3H); 1.27 (s, 3H); 1.38 (s, 9H); 2.47 (s, 3H); 2.72 (d, 3H); 2.98 (s, 3H); 5.06 (dd, 1H); 5.67 (dd, 1H); 6.08 (d, 1H).

5

((3E)-4-(((1R)-2-(Benzo[b]thiophen-3-yl)-1-(methyl-(1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature.

10 Water (5 mL) was added. Methylene chloride (8 mL), an aqueous solution of sodium hydrogen carbonate (saturated), sodium hydrogen carbonate (solid) was added until pH 8. The aqueous phase was extracted with methylene chloride (3 x 10 mL) and the combined organic phases were dried (magnesium sulfate). The solvent was removed in vacuo to give 0.13 g of the title compound.

15

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 6H); 2.47, (s, 3H); 2.75 (d, 3H); 2.96 (s, 3H); 4.98 (dd, 1H); 5.89 (dd, 1H); 6.10 (d, 1H).

PDMS : m/z 535.7 (M+H)⁺

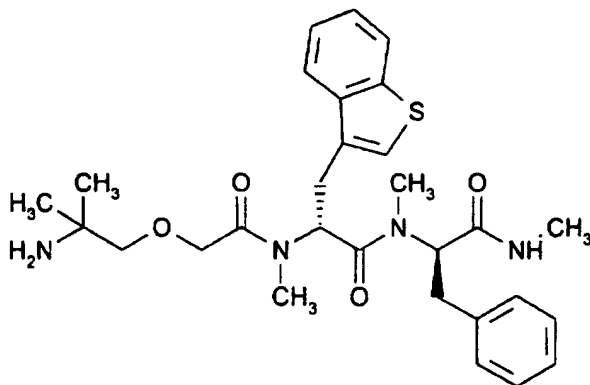
20

HPLC : R_t = 30.87 min (Method A1)

Example 22

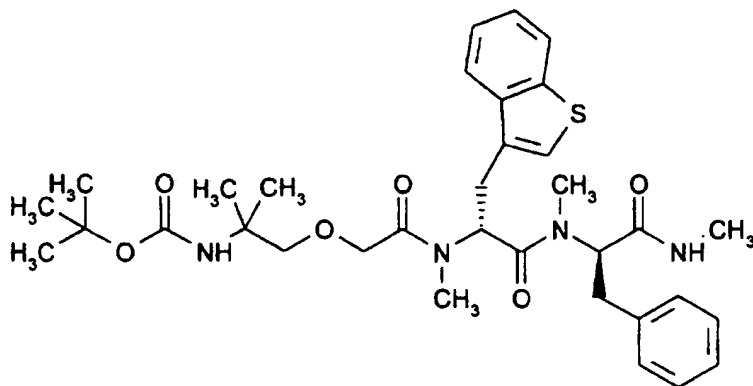
(2R)-2-(((2-Amino-2-methylpropoxy)acetyl)methyl- amino)-3-(benzo[b]thiophen-3-yl)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide:

5



(2-(((1R)-2-(Benzo[b]thiophen-3-yl)-((methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl carbamoyl)methoxy)-1,1-dimethylethyl)-carbamic acid tert butyl ester:

10



15 (2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid (0.193 g ; 0.78 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.11 g; 0.78 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.16 g; 0.86 mmol) were added. The reaction mixture was stirred for 15 min at

room temperature. (2R)-3-(Benzo[b]thiophen-3-yl)-N-methyl-2-methylamino-N-((1R)-1-methylcarbamoyl-2-phenylethyl)propionamide (0.32 g ; 0.78 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropylethylamine (0.13 mL; 0.78 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added. The reaction was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 20 mL) and an aqueous solution of sodium hydrogen carbonate (saturated; 20 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.44 g of (2-((((1R)-2-(benzo[b]thiophen-3-yl)-1-((methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-ethyl)methyl carbamoyl)methoxy)-1,1-dimethylethyl)carbamic acid tert butyl ester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.25 (s, 3H); 1.28 (s, 3H); 1.42 (s, 9H); 2.70 (s, 3H); 2.78 (d, 3H); 2.97 (s, 3H); 4.99 (dd, 1H); 5.88 (dd, 1H).

(2-((((1R)-2-(Benzo[b]thiophen-3-yl)-1-((methyl-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)methyl- carbamoyl)methoxy)-1,1-dimethylethyl)-carbamic acid tert butyl ester (0.435 g; 0.68 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 5 min at room temperature. Water (5 mL) was added. Methylene chloride (8 mL), an aqueous solution of sodium hydrogen carbonate (saturated) and solid sodium hydrogen carbonate was added until pH 8. The aqueous phase was washed with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo to afford 0.36 g of the title compound.

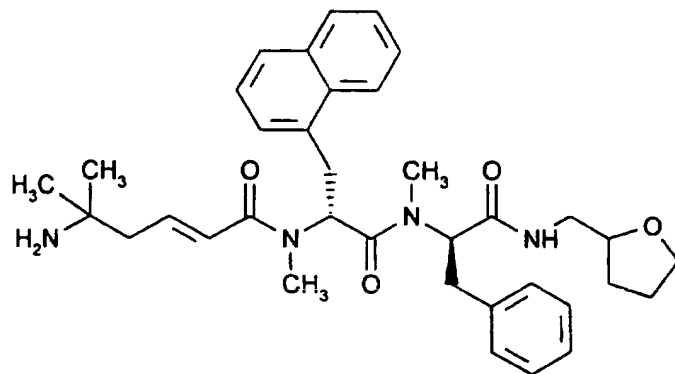
¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.25 (s, 6H); 2.65 (s, 3H); 2.75 (s, 3H); 2.98 (s, 3H); 4.68 (dd, 1H); 5.79 (dd, 1H).

HPLC : R_t = 30.35 min (Method A1)

PDMS : m/z 538.1 (M+H)⁺

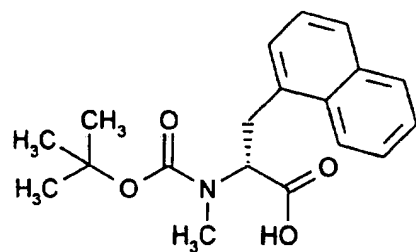
5 Example 23

(2E)-5-Amino-5-methylhex-2-enoic acid methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)-amide:



10

(2R)-2-(tert-Butoxycarbonylmethylamino)-3-(1-naphthyl)-propionic acid:



15

2-tert-Butoxycarbonylamino-3-(1-naphthyl)propionic acid (5.0 g; 0.015 mol) was dissolved in tetrahydrofuran (40 mL). Iodomethane (7.6 mL; 0.12 mol) was added. The reaction mixture was cooled to 0 °C and sodium hydride was added. The reaction mixture was stirred for 48 hours. Ethyl acetate (50 mL) and water (20 mL) were added dropwise. The solvent was removed in vacuo and ether (30 mL) and

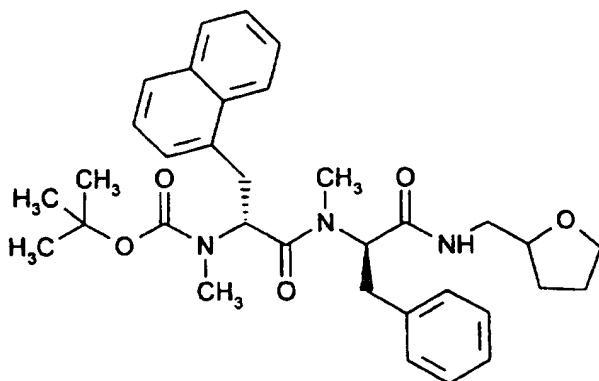
20

water (20 mL) were added. The organic phase was washed with an aqueous solution of sodium hydrogen carbonate (pH 8 ; 30 mL). To the aqueous phases was added citric acid (5%) to pH 3. The aqueous phase was extrated with ethylacetate (3 x 30 mL). The combined organic phases were washed with water (2 x 40 mL), an
5 aqueous solution of sodiumthiosulfate (5 % ; 40 mL) and water (40 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and ether (10 mL) and dicyclohexylamine (8.5 mL) were added. The precipitated crystals were filtered off and dissolved in water (20 mL). Hydrochloric acid was added to pH 2. The reaction mixture was extrated with ethyl acetate (4 x 40 mL), dried (magnesium sulfate) and
10 evaporated in vacuo to afford 3.97 g of (2R)-2-(tert-butoxycarbonyl methylamino)-3-(1-naphthyl)propionic acid.

¹H-NMR : (CDCl₃) δ 1.01 (s, 9H); 2.76 (s, 3H); 3.32 (dd, 1H); 3.93 (dd, 1H); 4.95 (dd, 1H); 7.30-8.10 (7 arom. H)

15

Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)-carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert-butylester:



20 (2R)-2-(tert-Butoxycarbonylmethylamino)-3-(1-naphthyl)-propionic acid (0.68 g; 2.06 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazol (0.28 g; 2.06 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.43 g; 2.26 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.

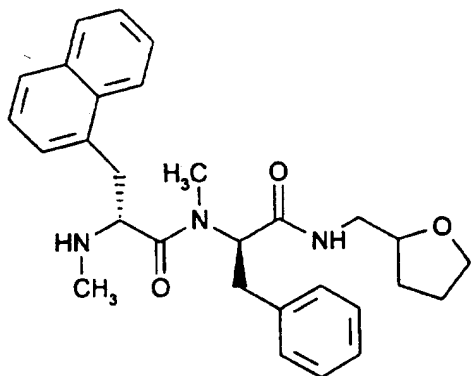
(2R)-2-Methylamino-3-phenyl-N-((2-tetrahydrofuranyl)-methyl)propionamide (0.54 g; 2.058 mmol) was dissolved in methylene chloride (10 mL) and added.

Diisopropylethylamine (0.35 mL; 2.06 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (10 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10%; 30 mL), an aqueous solution of sodium hydrogen carbonate (pH 8; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (5 x 50 cm) using ethyl acetate/methylene chloride 1:1 as eluent to afford 1.08 g of methyl-((1R)-1-(methyl-
 10 ((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 0.71 (s, 9H); 1.64 (s, 3H); 2.25 (s, 3H); 2.83 (d, 2H); 2.85 (s, 3H); 5.15 (dd, 1H); 5.44 (dd, 1H).

15

(2R)-N-Methyl-2-methylamino-3-(1-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide:



20

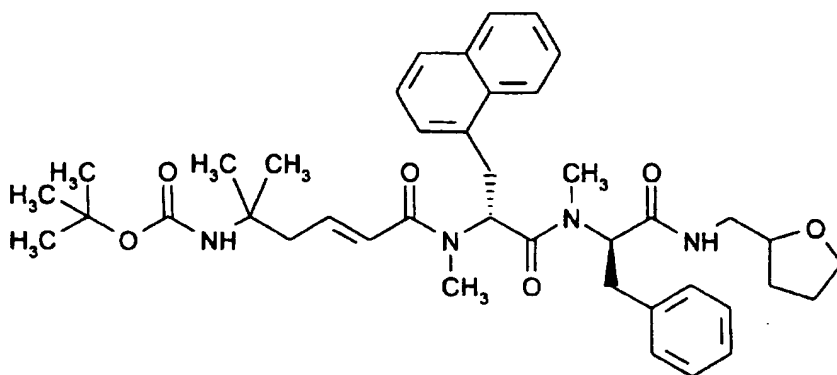
Methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)carbamic acid tert butylester (0.84 g; 1.46 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL)
 25 was added. The reaction mixture was stirred for 5 min at roomtemperature. Water

(3 mL) and methylene chloride (5 mL) was added. Sodium hydrogen carbonate (solid) was added until pH 8. The reaction mixture was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried (magnesium sulfate) and evaporated in vacuo to afford 0.68 g of (2R)-N-methyl-2-methylamino-3-(1-naphthyl)-N-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl-methyl)-carbamoyl)ethyl)propionamide.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.75 (s, 3H); 2.08 (s, 3H); 2.40 (d, 2H); 2.95 (d, 3H); 4.45 (m, 1H); 5.45-5.50 (m, 2H).

10

((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-carbamoyl)-2(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester:



15

(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (0.344 g; 1.41 mmol) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.19 g; 1.41 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.298 g; 1.56 mmol) were added. The reaction mixture was stirred for 15 min at room temperature. (2R)-N-Methyl-2-methylamino-3-(1-naphthyl)-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-propionamide (0.67 g; 1.42 mmol) was dissolved in methylene chloride (10 mL) and added. Diisopropyletamine (0.242 mL; 1.41 mmol) was added. The reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (20 mL) was added. The reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (

25

10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate (pH 8 ; 30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 30 cm) using methylene chloride/ethyl acetat (1:1) as eluent to afford 0.81 g of ((3E)-1,1-dimethyl-4-(methyl-((1R)-1-(methyl-
5 ((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2(1-naphthyl)ethyl)-carbamoyl)but-3-enyl)carbamic acid tert butylester.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.28 (s, 9H); 1.47 (s, 6H); 2.90 (d, 3H); 6.06 (d, 1H).

10

((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)-carbamoyl)-2(1-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester (0.80 g; 1.15 mmol) was dissolved in methylene chloride (3 mL) and trifluoroacetic acid (2 mL) was added. The reaction mixture was
15 stirred for 5 min at room temperature. Methylene chloride (5 mL) and sodium hydrogen carbonate were added until pH 8. The reaction mixture was extracted with methylene chloride (3 x 10 mL). The combined organic phases were dried (magnesium sulfate) and evaporated in vacuo to afford 0.50 g of the title compound.

20

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 6H); 2.25 (d, 2H); 2.08 (s, 3H); 2.89 (d, 3H); 3.18 (s, 3H); 5.90 (dd, 1H); 6.65 (d, 1H).

PDMS: m/z 599.8 (M+H)⁺

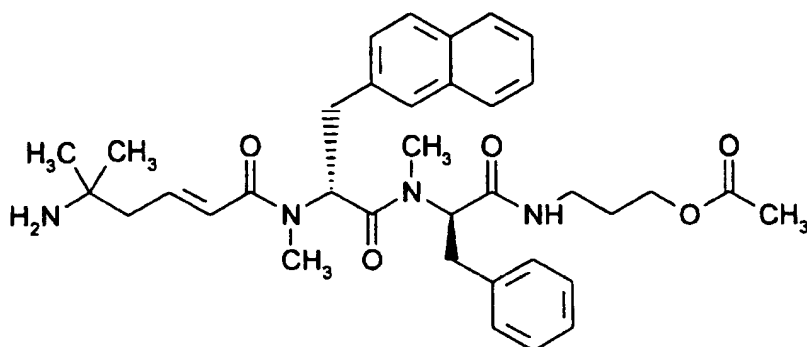
25

HPLC : R_t = 33.50 (Method A1)

Example 24

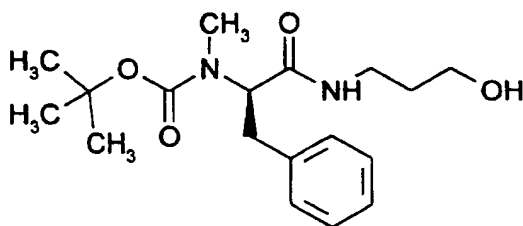
30

3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



5

N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester:



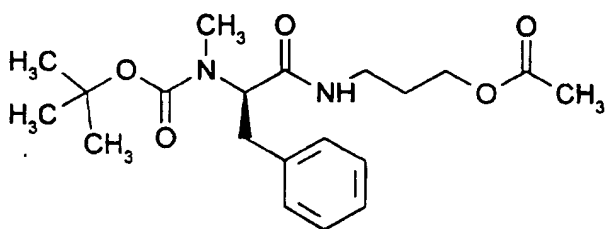
10

3-Aminopropan-1-ol (0.39 mL, 5.12 mmol) was added at room temperature to a solution of N-tert-butoxycarbonyl-N-methyl-D-phenylalanine (1.30 g, 4.65 mmol) in N,N-dimethylformamide (40 mL). 1-Hydroxybenzotriazole monohydrate (0.63 g, 4.65 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.89 g, 4.65 mmol) were added successively. The reaction mixture was stirred for 22 h at room temperature. It was diluted with 10% sodium hydrogensulfate solution (300 mL) and extracted with ethyl acetate (4 x 100 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica (45 g) with dichloromethane/methanol (10:1) to give 1.01 g of N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃): d 1.30 and 1.40 (both s, together 9 H); 1.65 and 1.72 (both br, together 2 H); 2.77 (s, 3 H); 2.90 - 3.75 (m, 6 H); 4.75 and 4.86 (both m, together 1 H); 6.50 (m, 1 H); 7.10 - 7.25 (m, 5 H).

5

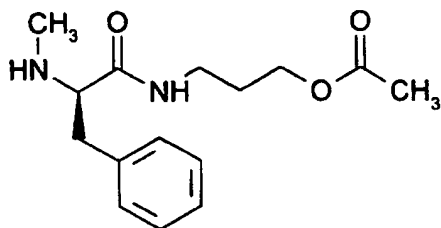
3-((2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-phenylpropionylamino)propyl acetate:



- 10 A solution of N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamic acid tert-butylester (965 mg, 2.86 mmol) in dichloromethane (10 mL) was cooled to 0°C. 4-(dimethylamino)pyridine (35 mg, 0.29 mmol), triethylamine (0.60 mL, 4.29 mmol), and acetic acid anhydride (0.32 mL, 3.43 mmol) were added. The reaction mixture was stirred for 5 hours, while it was warming slowly to room
- 15 temperature. The reaction mixture was diluted with dichloromethane (100 mL) and washed with 10% sodium hydrogensulfate solution. The aqueous phase was extracted with dichloromethane (2 x 50 mL). The organic phases were combined and washed with saturated sodium hydrogen carbonate solution. They were dried over magnesium sulfate. The solvent was removed in vacuo, and the crude product
- 20 was purified by flash chromatography on silica (90 g) with ethyl acetate/dichloromethane (1:3 to 1:1) to give 890 mg of 3-((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropionylamino)propyl acetate.

¹H-NMR (CDCl₃) d 1.25 and 1.39 (both s, together 9 H); 1.85 (m, 2 H); 2.06 and 2.07 (both s, together 3 H); 2.76 (s, 3 H); 2.95 (m, 1 H); 3.35 (m, 3H); 4.00 - 4.20 (m, 2 H); 4.70 - 4.87 (both m, together 1 H); 6.22 and 6.37 (both br, together 1 H); 7.10 - 7.35 (m, 5 H).

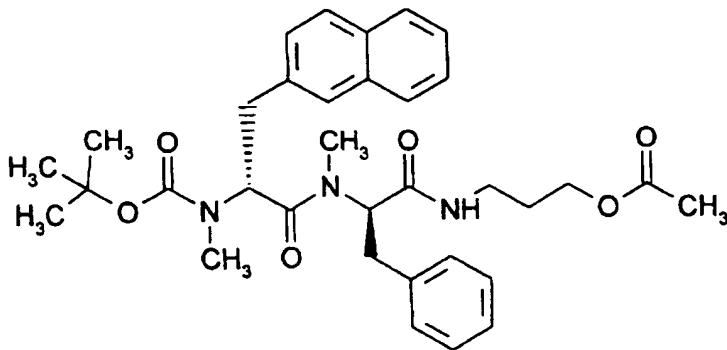
3-((2R)-2-(Methylamino)-3-phenylpropionylamino)propyl acetate:



5 A solution of 3-((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropionylamino)propyl acetate (862 mg, 2.28 mmol) in dichloromethane (3 mL) was cooled to 0°C. Trifluoroacetic acid (3 mL) was added. The solution was stirred for 10 min. The solvents were removed in vacuo without warming. The residue was dissolved in dichloromethane (50 mL) and the solvent was removed in vacuo. The
 10 procedure was repeated twice. The crude product was purified by flash chromatography on silica (70 g) with dichloromethane/methanol/25% ammonia in water (100:10:1) to give 602 mg of 3-((2R)-2-(methylamino)-3-phenylpropionylamino)propyl acetate.

15 ¹H-NMR (CDCl₃) δ 1.85 (m, 2 H); 2.07 (s, 3 H); 2.80 (s, 3 H); 2.72 (dd, 1 H); 3.20 (m, 2 H); 3.35 (m, 2 H); 4.10 (t, 1 H); 7.15 - 7.40 (m, 6 H).

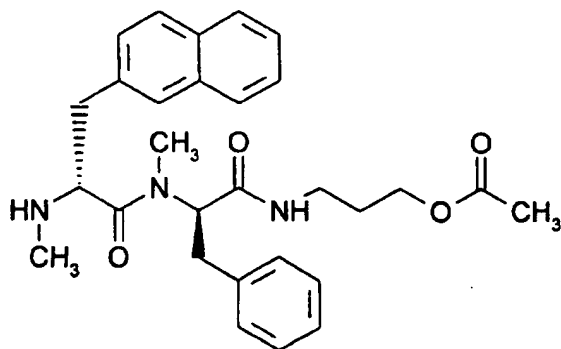
3-((2R)-2-(N-((2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)-propionic acid (659 mg, 2.0 mmol) was dissolved in N,N-dimethylformamide (3 mL) and dichloromethane (3 mL). The solution was cooled to 0°C. 1-Hydroxy-7-azabenzotriazole (272 mg, 2.0 mmol) was added. After 10 min N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (460 mg, 2.4 mmol) was added. The reaction mixture was stirred for 10 min. A solution of 3-((2R)-2-(methylamino)-3-phenylpropionylamino)propyl acetate (567 mg, 2.0 mmol) in dichloromethane (4 mL) was added. The solution was stirred for 16 hours, while the temperature rose to room temperature. The reaction mixture was diluted with ethyl acetate (150 mL). It was extracted with 10% sodium hydrogensulfate solution (150 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and the organic phases were combined and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (70 g) with ethyl acetate/heptane (2:1) to give 973 mg of 3-((2R)-2-(N-((2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)-propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate.

¹H-NMR (CDCl₃): d 4.99, 5.11, 5.18, 5.35, and 5.42 (all dd, together 2 H); 5.75 and 6.15 (both t, together 1 H).

3-((2R)-2-(N-((2R)-2-Methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:



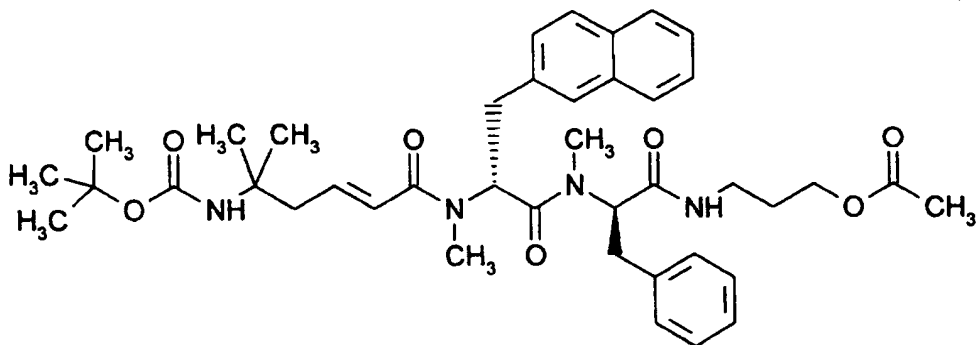
At 0°C, trifluoroacetic acid (3 mL) was added to a solution of 3-((2R)-2-(N-((2R)-2-

(N-(tert-butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate (885 mg, 1.50 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 5 min. The solvents were removed in vacuo at 20°C. The residue was dissolved in dichloromethane (40 mL). The
 5 procedure was repeated twice. The crude product was purified by flash chromatography on silica (45 g) with dichloromethane/methanol/25% solution of ammonia in water (100:10:1) to give 497 mg of 3-((2R)-2-(N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate.

10 ¹H-NMR (DMSO-d₆): d 1.65 (m, 2 H); 2.01 and 2.02 (both s, together 3 H); 4.67 and 5.35 (both dd, together 1 H).

3-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate:

15



20

(2E)-5-tert-Butoxycarbonylamino-5-methylhex-2-enoic acid (277 mg, 1.14 mmol) and 1-hydroxy-7-azabenzotriazole (155 mg, 1.14 mmol) were dissolved in dichloromethane (3 mL) and N,N-dimethylformamide (3 mL). The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (254
 25 mg, 1.32 mmol) was added. The solution for stirred for 10 min at 0°C, before a

solution of 3-((2R)-2-(N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate in dichloromethane (3 mL) was added. The solution was stirred for 18 hours, while it was warming up slowly to room temperature. It was diluted with ethyl acetate (100 mL) and extracted with
5 10% sodium hydrogensulfate solution. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (45 g) with ethyl acetate/heptane (2:1) to give 427 mg of
10 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate.

¹H-NMR (CDCl₃): d 1.80 (m, 2 H); 4.10 (m, 2 H); 6.05 (m, 1 H); 6.75 (m, 1 H).

15 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate (412 mg, 0.58 mmol) was dissolved in dichloromethane (2 mL). The solution was cooled to 0 °C. Trifluoroacetic acid (2
20 mL) was added. The solution was stirred for 8 min at 0 °C, and the solvents were removed in vacuo with a water bath temperature of 20°C. The residue was dissolved in dichloromethane (30 mL) and the solvent was removed in vacuo. This latter procedure was repeated twice. The crude product was purified by flash chromatography on silica (35 g) with dichloromethane/methanol/25% ammonia in
25 water (100:10:1). The product was dissolved in ethyl acetate (3 mL) and 3M hydrogen chloride in ethyl acetate (0.7 mL) was added. The solvent was removed in vacuo and the product was dried over night in vacuo to give 0.21 g of title compound as a hydrochloride.

30 ¹H-NMR (DMSO-d₆) (selected values) d 1.70 (m, 2H); 4.00 (m, 2H).

MS: found: 616.3 ± 1 $[M+1]^+$

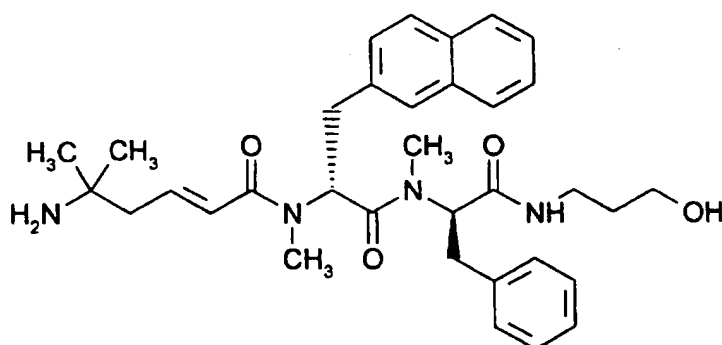
HPLC: $R_T = 20.47$ min (method A1)

5

Example 25

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methyl-

10 amide:



15 3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-anaphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate hydrochloride (140 mg, 0.21 mmol) was dissolved in 1,4-dioxane (3 mL). A solution of lithium hydroxide (18 mg, 0.74 mmol) in water (1.5 mL) was added. Water was added until a clear solution was obtained. The reaction mixture was stirred for 16 h

20 at room temp. It was diluted with water (30 mL) and extracted with tert-butylmethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed in vacuo. The residue was dissolved in water (15 mL) and acetic acid (0.8 mL) and the resulting solution was lyophilized to give 105 mg of the acetate salt of the title compound.

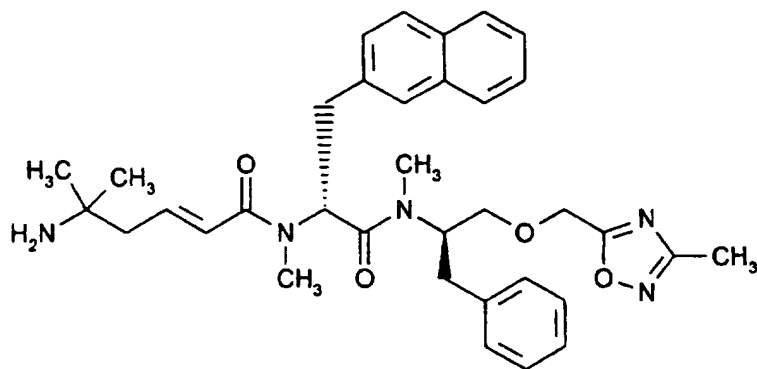
¹H-NMR (DMSO-d₆) (selected peaks): d 0.95 (s, 6 H); 1.55 (m, 3H); 3.42 (m, 2H).

HPLC: R_T = 30.97 min (method A1)

5

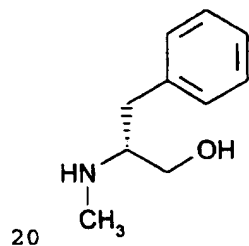
Example 26

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
10 (((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



15

(2R)-2-(Methylamino)-3-phenylpropan-1-ol:



20

(2R)-2-(Methylamino)-3-phenylpropan-1-ol was prepared analogue to M. J.

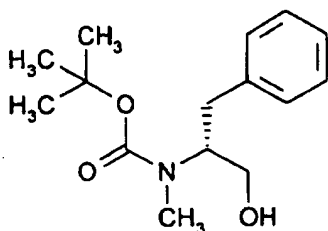
McKennon and A. I. Meyers J. Org. Chem. 1993 (58), 3568 - 3571. m.p. 69 - 69°C

(lit: A. I. Meyers, J. Org. Chem. 1993 (58), 3568 - 3571: 71 - 74 °C; A. Karim, A.

Mortreux, F. Petit, G. Buono, G. Pfeiffer, C. Siv, J. Organomet. Chem. 1986, 317,

5 93: 68 °C, for (2S)-2-(methylamino)-3-phenylpropan-1-ol)

N-((1R)-1-Hydroxymethyl-2-phenylethyl)-N-methyl carbamaic acid tert-butylester:



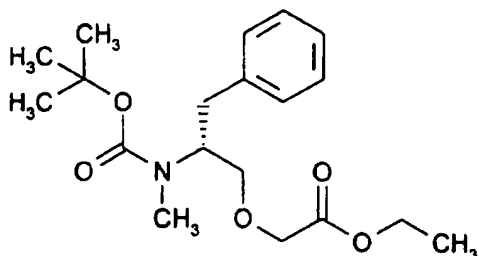
10 (2R)-2-(Methylamino)-3-phenylpropan-1-ol (6.00 g, 36.3 mmol) was dissolved in Tetrahydrofuran (80 mL). 1N sodium hydroxide solution (36.3 mL, 36.3 mmol) was added. A solution of di-tert.-butyl dicarbonate (9.50 g, 43.6 mmol) in tetrahydrofuran (60 mL) was slowly added at room temperature. The solution was stirred 16 h at room temperature. Water (200 mL) and ethyl acetate (200 mL) were added. The

15 phases were separated. The aqueous phase was washed with ethyl acetate (2 x 100 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed in vacuum. The product was purified on silica (170 g) with ethyl acetate/heptane (1:1) to give 7.85 g (81%) of N-((1R)-1-hydroxymethyl-2-phenylethyl)-N-methyl carbamaic acid tert-butylester.

20

¹H-NMR (CDCl₃): δ = 1.32 - 1.40 (br, 9H); 2.55 - 2.95 (m, 5 H); 3.65 - 3.67 (br, 2 H); 4.10 - 4.35 (br, 1H); 7.05 - 7.35 (m, 5 H).

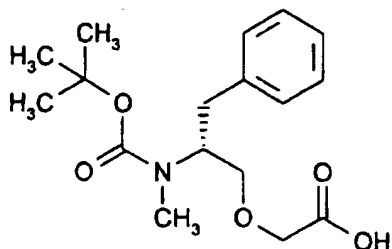
25 ((2R)-2-(tert-Butoxycarbonylmethylamino)-3-phenylpropoxyl)acetic acid ethyl ester:



N-((1R)-1-Hydroxymethyl-2-phenylethyl)-N-methyl carbamaic acid (3.98 g, 15.0 mmol) was dissolved in 1,2-dichloroethane (150 mL). The solution was warmed to 75 - 80 °C. Rhodium(II) acetate (0.1 g, 0.4 mmol) was added. During a period of 6 hours a solution of ethyl diazoacetate (2.4 mL, 22.5 mmol) in dichloromethane (100 mL) was added. After 3 h another portion of rhodium(II) acetate (0.1 g, 0.4 mmol) was added. After addition of ethyl diazoacetate, the solution was cooled to room temperature. It was filtered through a plug of celite. The solvent was removed in vacuum. The crude product was chromatographed on silica (100 g) to give 1.53 g of ((2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropoxyl)acetic acid ethyl ester.

¹H-NMR (CDCl₃): δ = 1.28 (m, 3 H); 1.39 and 1.48 (both s, together 9H); 2.65 - 2.95 (m, 9 H); 3.58 (m, 1 H); 3.67 (br, 1H); 3.98 - 4.27 (m, 4 H); 4.35 - 4.55 (br, 1H); 7.10 - 7.30 (m, 5 H).

((2R)-2-(tert-Butoxycarbonylmethylamino)-3-phenylpropoxy)-acetic acid:

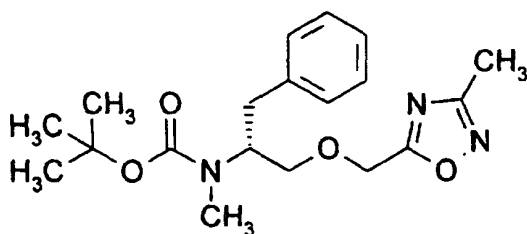


((2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropoxyl)-acetic acid ethyl ester (0.60 g, 1.71 mmol) was dissolved in dioxane (5 mL). A solution of lithium hydroxide

(0.05g, 2.20 mmol) in water (2 mL) was added. The solution was stirred at room temperature for 56 hours. Ethyl acetate (10 mL) and water (2 mL) were added. The phases were separated. The aqueous phase was extracted with ethyl acetate (10 mL). The combined organic layers were extracted with 1N sodium hydroxide solution (20 mL). The combined aqueous phases were acidified with a 1M sodium hydrogensulfate solution (pH 2) and extracted with ethyl acetate (2 x 20 mL). These ethyl acetate layers were combined and dried over magnesium sulfate. The solvent was removed in vacuum to give 0.38 g of crude ((2R)-2-(tert-butoxycarbonylmethylamino)-3-phenylpropoxy) acetic acid, which was used for the following steps.

¹H-NMR (DMSO *d*₆): δ = 1.15 and 1.27 (both s, together 9H); 2.55 - 2.70 (m, 5 H); 3.45 - 3.65 (m, 2 H); 4.00 - 4.10 (m, 2 H); 4.30 - 4.50 (m, 1H); 7.15 - 7.35 (m, 5 H); 13.60 (br, 1H).

N-Methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl-2-phenylethyl)carbamoyl)acetic acid tert-butylester:



20

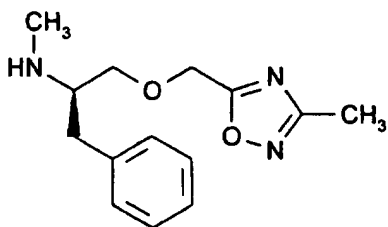
At -13 °C, isobutyl chloroformate (0.80 mL, 6.19 mmol) was added slowly to a solution of ((2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropoxy)acetic acid (2.0 g, 6.18 mmol) and N-methylmorpholine (0.68 mL, 6.18 mmol) in tetrahydrofuran (25 mL). The solution was stirred for 15 min at this temperature. Acetamidoxim (0.92 g, 12.36 mmol) was added as a solid. Immediately after addition, N-methylmorpholine (0.68 mL, 6.18 mmol) was given to the reaction mixture. It was stirred for 45 min at -13°C, 3.5 h at room temperature and 16 hours at reflux. The reaction mixture was cooled to room temperature and diluted with

ethyl acetate (100 mL). It was extracted with water and 10% sodium hydrogensulfate solution (10 mL/40 mL). The aqueous phase was extracted with ethyl acetate (2x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate.

- 5 The solvent was removed in vacuo. The crude product was purified on silica (90 g) with ethyl acetate/heptane (1:1) as eluent to give 1.17 g of N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl-2-phenylethyl)carbamcic acid tert-butylester.

- 10 ¹H-NMR (CDCl₃) δ 1.31 and 1.39 (both s, together 9H); 2.43 (s, 3H); 2.65 - 2.95 (m, 5H); 3.65 (m, 1H); 3.76 (m, 1H); 4.43 and 4.53 (both br, together 1H); 4.70 - 4.80 (m, 2H); 7.10 - 7.35 (m, 5H).

- 15 3-Methyl-5-(((2R)-2-(methylamino)-3-phenylpropoxy)methyl)-1,2,4-oxadiazole:

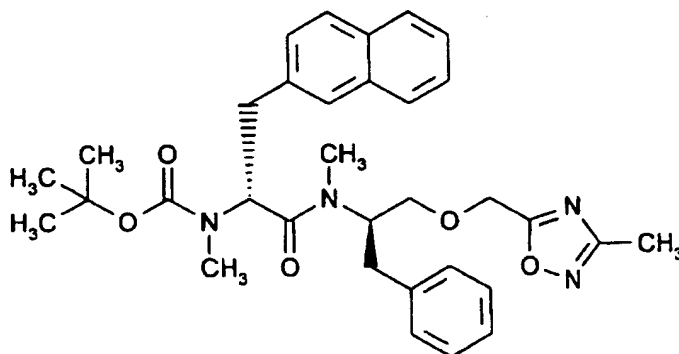


- 20 N-Methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl-2-phenylethyl)carbamcic acid tert-butylester (1.13 g; 3.13 mmol) was dissolved in dichloromethane (3 mL). The solution was cooled to 0°C. Trifluoroacetic acid (3 mL) was added. The solution was stirred at 0 °C for 5 min. The solvent was removed in vacuo without warming. The residue was dissolved in dichloromethane (100 mL)
- 25 and the solvent was removed in vacuo. This procedure was repeated twice. The crude product was purified by flash chromatography on silica (70 g) with dichloromethane/methanol/25% aqueous ammonia (100:10:1) to give 0.75 g of 3-methyl-5-(((2R)-2-(methylamino)-3-phenylpropoxy)methyl)-1,2,4-oxadiazole.

¹H-NMR (CDCl₃) δ 2.40 (s, 3H); 2.45 (s, 3H); 2.75 (dd, 1H); 2.85 (dd, 2H); 2.93 (m, 1H); 3.48 (dd, 1H); 3.56 (dd, 1H); 4.70 (AB, 2H); 7.15 - 7.35 (m, 5H)).

5

N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butylester:



10

(2R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(2-naphthyl)propionic acid (701 mg, 2.68 mmol) was dissolved in dichloromethane (4 mL) and N,N-dimethylformamide (4 mL). The solution was cooled to 0°C. 1-Hydroxy-7-azabenzotriazole (365 mg, 2.68 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (617 mg, 3.22 mmol) were successively added.

15

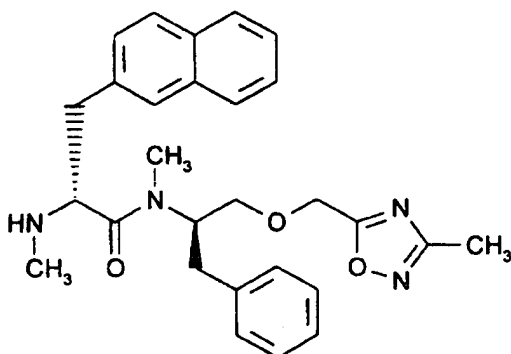
The solution was stirred for 15 min at 0 °C. A solution of 3-methyl-5-(((2R)-2-(methylamino)-3-phenylpropoxy)methyl)-1,2,4-oxadiazole (701 mg, 2.68 mmol) in dichloromethane (4 mL) was added. The reaction mixture was stirred for 16 hours, while the temperature slowly rose to room temperature. It was diluted with ethyl acetate (100 mL) and extracted with a mixture of saturated sodium chloride solution (50 mL) and water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (90 g) with ethyl acetate/heptane (2:1) to give 1.23 g of N-methyl-N-((1R)-1-

25

(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butylester.

- 5 ¹H-NMR (CDCl₃) δ 0.95, 1.02, 1.13, and 1.26 (all s, together 9H); 2.35 - 2.45 (m, 3H); 7.00 - 7.80 (m, 12H).

- (2R)-2-(Methylamino)-3-(2-naphthyl)propionic acid N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)amide:
- 10

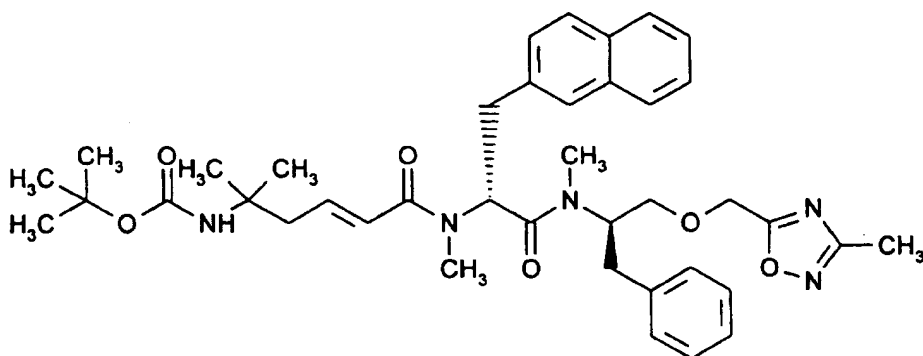


- N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butylester (1.21 g, 2.12 mmol) was dissolved in dichloromethane (4 mL). The solution was cooled to 0 °C. Trifluoroacetic acid (4 mL) was added. The solution was stirred for 12 min at 0 °C. The solvent was removed in vacuo without warming. The residue was dissolved in dichloromethane (150 mL), and the solvent was removed in vacuo. This latter procedure was repeated twice. The crude product was purified by flash chromatography on silica (70 g) with dichloromethane/methanol/25% aqueous ammonia (200:10:1) to give 497 mg of (2R)-2-(methylamino)-3-(2-naphthyl)propionic acid N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)amide.
- 15
- 20

¹H-NMR (DMSO d₆) δ 1.67 and 1.92 (both s, together 3H); 2.32 and 2.34 (both s, together 3H); 2.71 and 2.86 (both s, together 3H); 4.60 and 4.79 (both s, together 2H); 7.05 - 7.90 (m, 12H).

5

(3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)-carbamoyl)but-3-enylcarbamate tert-butylester:



10

(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (258 mg, 1.06 mmol) was dissolved in dichloromethane (3 mL) and N,N-dimethylformamide (3 mL). 1-Hydroxy-7-azabenzotriazole (144 mg, 1.06 mmol) was added. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (260 mg, 1.36 mmol) was added. The solution was stirred for 15 min at 0 °C. A solution of (2R)-2-(methylamino)-3-(2-naphthyl)propionic acid N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)-methyl)-2-phenylethyl)amide (456 mg, 0.97 mmol) in dichloromethane (3 mL) was added. The reaction mixture was stirred for 16 h, at room temperature. The reaction mixture was diluted with ethyl acetate (150 mL). It was washed with saturated sodium chloride solution (150 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (60 g) with ethyl acetate/heptane (2:1) to give 514 mg of (3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-

25

methyl-1,2,4-oxadizol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃) δ 1.05 - 1.50 (m, 15H); 6.05 (m, 1H); 6.55 and 6.74 (both m,
5 together 1H); 7.05 - 7.85 (m, 12H).

(3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadizol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)-carbamoyl)but-3-enylcarbamic acid tert-butylester (464 mg, 0.66 mmol) was
10 dissolved in dichloromethane (2 mL). The reaction mixture was cooled to 0 °C. Trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 7 min at 0 °C. The solvent was removed in vacuo. The residue was dissolved in dichloromethane (50 mL), and the solvent was removed in vacuo. This latter procedure was repeated two times. The crude product was purified by flash
15 chromatography on silica (30 g) with dichloromethane/methanol/25% aqueous ammonia (100:10:1). The product was dissolved in ethyl acetate (3 mL) and 3 M hydrogen chloride in ethyl acetate (0.7 mL) was added. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate (50 mL) and the solvent was removed in vacuo to give 285 mg of the title compound as a hydrochloride.

20

HPLC: R_t = 35.40 min (Method A1)

¹H-NMR (DMSO-d₆) δ 1.03, 1.04, and 1.15 (all s, together 6H); 2.35 and 2.36 (both s, together 3H).

25

MS: 598.3 ([M+1]⁺)

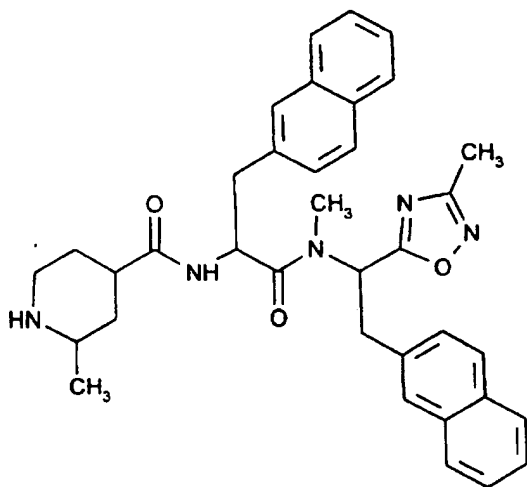
C₃₅H₄₄N₅ClO₄ · 2H₂O

calc. C62.72 H7.22 N10.45

30 found C62.72 H7.04 N10.30

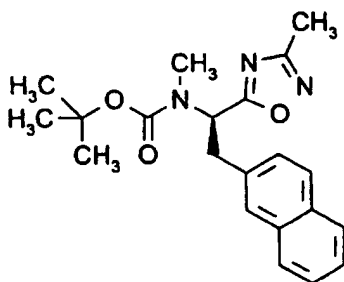
Example 27

- 5 2- Methyl-piperidine-4-carboxylic acid N-{1-[N-methyl-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl)carbamoyl]-2-(2-naphthyl)ethyl} amide:



10

(R) N-Methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamic acid
tertbutyl ester:

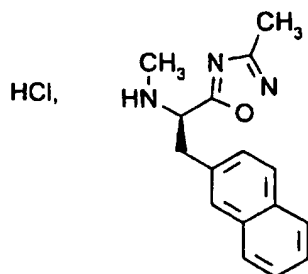


15

iso-Butylchloroformate (1.22 g, 9.0 mmol) was dropwise added to a solution of (R)
N-methyl-N-tert-butoxycarbonyl-3-(2-naphthyl)alanine (3.0 g, 9 mmol) and N-

methylmorpholine (0.91 g, 9.0 mmol) in dichloromethane (40mL) at -20 °C. After 15 min at -20 °C acetamidoxim (1.33 g, 18 mmol) was added followed by addition of N-methyl-morpholine (0.91 g, 9 mmol). After 30 min at -20 °C the reaction mixture was heated to 20 °C and diluted with N,N-dimethylformamide (40 mL). The
5 dichloromethane was evaporated in vacuo and the reaction mixture was heated at 120° C for 16 hours. The reaction mixture was poured into water (120 mL) and extracted with ethyl acetate (180 mL). The organic phases were collected, washed with water (40 mL) and dried (magnesium sulfate). The solution was concentrated in vacuo to give 3.5 g of crude (R) N-methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-
10 (2-naphthyl)ethyl]carbamic acid tertbutyl ester that was used without further purification.

(R) N-Methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]amine
15 hydrochloride:



(R) N-Methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamic acid tertbutyl ester (3.3 g, 9.0 mmol) was dissolved in a saturated solution of hydrogen chloride in ethyl acetate (75 mL). After 3 hours at 20 °C the reaction mixture was
20 filtered to give 1.52 g of (R) N-methyl-N-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]amine hydrochloride.

m.p. 198-202 °C.

25 ¹H-NMR (DMSO-d₆) δ 2.35(s, 3H); 2.68(s, 3H); 3.43(dd, 1H); 3.80(dd, 1H); 5.29(dd, 1H); 7.30(d, 1H); 7.45-7.90(m, 7H).

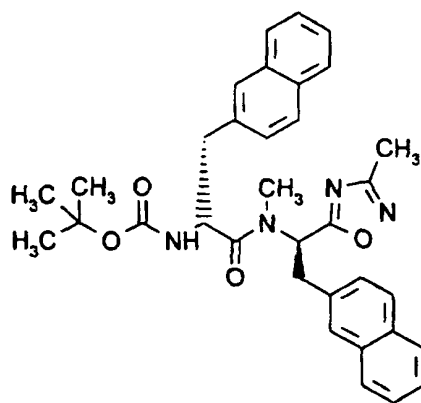
HPLC: $R_t = 16.3$ min (Method A1)

Calculated for $C_{16}H_{17}N_3O_1, HCl$:

C, 63.26; H, 5.97; N, 13.83%; found:

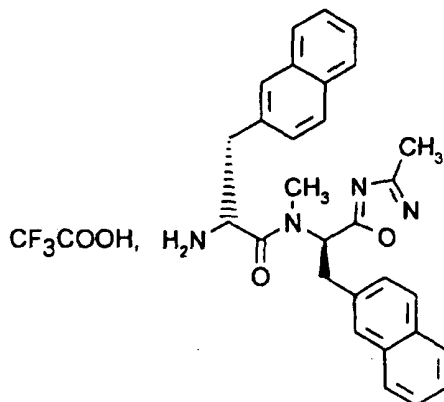
5 C, 63.37; H, 6.11; N, 13.53%.

{{(1R)-1-{N-Methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-carbamoyl}-2-(2-naphthyl)ethyl}carbamic acid tertbutyl ester:



- 10 N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (1.12 g, 5.85 mmol) and 1-hydroxy-7-azabenzotriazole (0.8 g, 5.85 mmol) were added to a solution of (R) N-tert-butoxycarbonyl-3-(2-naphthyl)alanine (1.84 g, 5.85 mmol) in N,N-dimethylformamide (45 mL). After 30 min at 20 °C a mixture of (R) N-methyl-N-{1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl}amine hydrochloride (1.27 g, 4.18 mmol) and triethylamine (0.42 g, 4.18 mmol) in N,N-dimethylformamide (15 mL) were added. After 18 hours at 20 °C the reaction mixture was poured on water (200 mL) and extracted several times with ethyl acetate (110 mL). The combined organic phases were washed with aqueous citric acid (10%, 40 mL), a saturated solution of sodium hydrogen carbonate (3x40 mL) and water (3x40 mL). After
- 20 drying (magnesium sulfate) the solvent was concentrated in vacuo to give 2.4 g of crude {{(1R)-1-{N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl}carbamic acid tertbutyl ester which was used for the next step without further purification.

(2R)-2-Amino-N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)-ethyl]-3-(2-naphthyl)propionamide (as a trifluoroacetate):



5 {(1R)-1-[N-Methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-carbamoyl]-2-(2-naphthyl)ethyl}carbamic acid tertbutyl ester (2.4 g, 4.2 mmol) was dissolved in a mixture of trifluoroacetic acid (40 mL) and dichloromethane (40 mL) at 20°C. After 10 min the reaction mixture was concentrated in vacuo and coevaporated from dichloromethane (80 mL). The residue was crystallised from
 10 ethyl acetate to give 1.19 g of (2R)-2-amino-N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)-ethyl]-3-(2-naphthyl)propionamide, trifluoroacetic acid.

mp 190-191°C.

15

¹H-NMR (DMSO-d₆) δ 2.33(s, 3H); 2.88(s, 3H); 3.00-3.15(m, 2H); 3.45(dd, 1H); 3.65(dd, 1H); 4.71(t, 1H); 7.25-7.95(m, 14H).

HPLC: R_f = 24.3 min (Method A1)

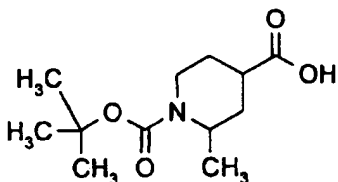
20

Calculated for C₂₈H₂₈N₄O₂·CF₃COOH:

C, 64.35; H, 5.05; N, 9.68%; found:

C, 64.30; H, 5.13; N, 9.44%.

2-Methylpiperidine-1,4-dicarboxylic acid 1-tert-butyl ester:



5

A suspension of 2-chloro-4-carboxy-6-methylpyridine (5.1 g, 3.0 mmol) in hydrochloric acid (1N, 50 mL) was hydrogenated over palladium on charcoal (20%, 0.95 g) at 150psi of hydrogen at 60°C for 18 hours. The reaction mixture was filtered and concentrated in vacuo. The crude product was dissolved in aqueous sodium hydroxide (1N, 53 mL) and a solution of di-tert-butyloxocarbonyl (6.35 g, 29.1 mmol) in tetrahydrofuran (30 mL) was added. After 3 days at room temperature the reaction mixture was extracted with diethyl ether (50 mL) at pH 10. The aqueous phase was adjusted to pH 2 with sulfuric acid (1N, 30 mL) and extracted with ethyl acetate (30 mL). The organic phase was washed with water (4x15 mL), dried (magnesium sulfate) and concentrated in vacuo. The residue was chromatographed on silica (105 g) using ethyl acetate and heptane (1:1) as eluent to give 1.8 g of 2-methylpiperidine-1,4-dicarboxylic acid 1-tert-butyl ester. M.p. 109-112°C

¹H-NMR (DMSO-d₆) δ 1.13(d, 3H); 1.42(s, 9H); 1.70(m, 1H); 1.95(m, 2H); 2.60(m, 1H); 3.12(m, 1H); 3.31(s, 1H); 3.77(m, 1H); 4.15(m, 1H); 12.25 (s, 1H).

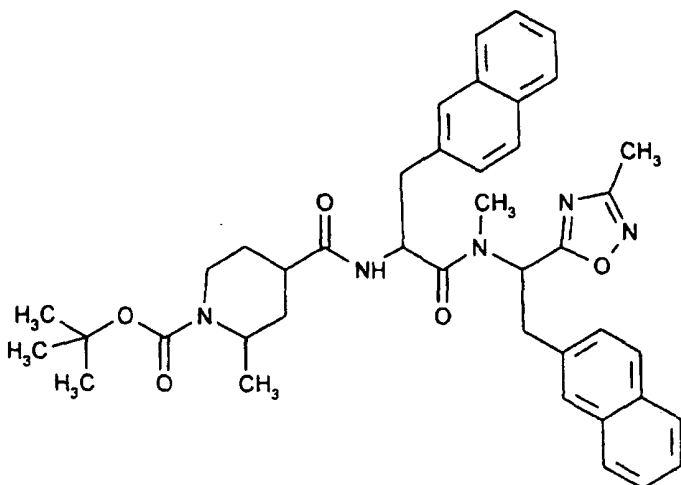
Calculated for C₁₂H₂₁N₁O₄:

C, 59.24; H, 8.70; N, 5.76%; found:

C, 59.39; H, 9.13; N, 5.58%.

25

4-(1-{Methyl-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)carbamoyl-2-methylpiperidine-1-carboxylic acid tert-butyl ester:



N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.46 g, 2.42 mmol) and 1-hydroxy-benzotriazole monohydrate (0.37 g, 2.41 mmol) were added to a solution of 2-methylpiperidine-1,4-dicarboxylic acid-1-tert-butylester (0.59 g, 2.42 mmol) in N,N-dimethylformamide (8 mL). After 30 min at 20°C a solution of (2R)-2-amino-N-methyl-N-[(1R)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-3-(2-naphthyl)propionamide (as a trifluoroacetate) (1.0 g, 1.73 mmol) and diisopropylethylamine (0.22 g, 1.73 mmol) in N,N-dimethylformamide (4 mL) was added. After 18h at 20°C the reaction mixture was poured on water (100 mL) and extracted several times with ethyl acetate (total 60 mL). The collected organic phases were washed with aqueous citric acid (10%, 20 mL), a saturated solution of sodium hydrogen carbonate (20 mL) and water (3x20 mL). After drying (magnesium sulfate) the solution was concentrated in vacuo to give 1.25g of crude 4-(1-{methyl-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)-carbamoyl-2-methylpiperidine-1-carboxylic acid tert-butyl ester that was used for the next step without further purification.

HPLC: R_f = 35.8min (Method A1)

20

4-(1-{Methyl-[1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl)-carbamoyl-2-methylpiperidine-1-carboxylic acid tert-butyl ester (1.25

g, 1.81 mmol) was dissolved in a mixture of trifluoroacetic acid (5 mL) and dichloromethane (5 mL). After 10 min at 20°C the reaction mixture was quenched with a saturated solution of sodium hydrogen carbonate (45 mL) and extracted with dichloromethane (60 mL). The organic phases were collected, dried (magnesium sulfate) and concentrated in vacuo. The residue was chromatographed on silica gel (105 g) using a 10% mixture of ammonia in ethanol and dichloromethane (1:9) as eluent to give 0.90 g of the title compound, which was finally lyophilysed in 10% acetic acid.

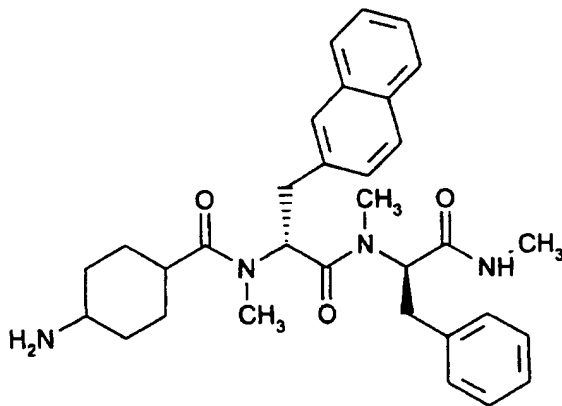
10 HPLC: $R_t = 24.3$ min (Method A1)

PDMS: calculated: 589.7 [M]

found: 589.5 ± 1 [M+1]

15 Example 28

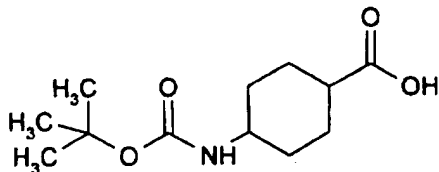
4-Amino-cyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl]-2-(2-naphtyl)ethyl)amide:



20

4-tert-Butoxycarbonylamino-cyclohexanecarboxylic acid:

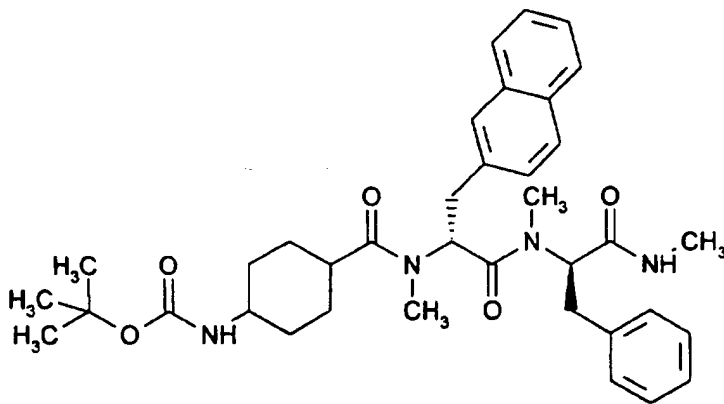
25



To a suspension of 4-aminocyclohexane carboxylic acid (3.0 g, 20.95 mmol) in
 5 dioxan (40 mL) and water (20 mL) was added 20 ml of a 1 M sodium hydroxide
 solution. Di-tert-butyl dicarbonate (5.0 g, 23.05 mmol) was added and the mixture
 was stirred overnight. The mixture was concentrated in vacuo to 30 ml of solvent
 and 60 ml of ethyl acetate was added and the mixture was cooled to 0°C. The
 mixture was acidified to pH 2 with sodium bisulfate and the aqueous phase was
 10 extracted with ethyl acetate (2 x 100 ml). The combined organic phases were
 washed with water (100 ml) and dried over magnesium sulfate and concentrated in
vacuo to give 4.13 g of 4-tert-butoxycarbonylamino cyclohexanecarboxylic acid.

1H-NMR (DMSO-d₆): d_H 1.3 (s, 9H) 1.3-1.6 (m, 5H) 1.9 (m, 3H), 2.3 (m, 1H) 6.7 (m,
 15 1H)

(4-[N-Methyl-N-((1R)-1-(N-methyl-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]-
 carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl]cyclohexyl)carbamic acid tert-butyl ester:



20

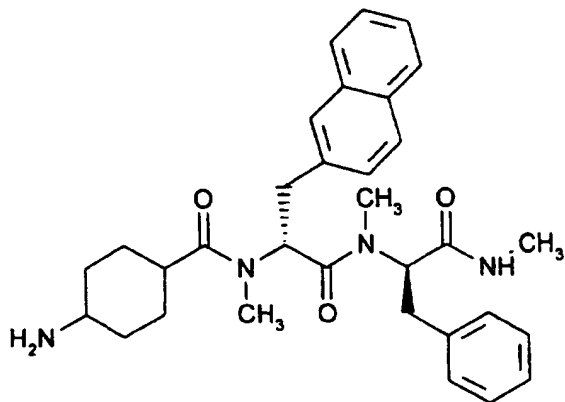
To a suspension of 4-tert-butoxycarbonylamino cyclohexanecarboxylic acid (115
 mg, 0.47) in 5 ml of dichloromethane was added 1-hydroxy-7-azabenzotriazole (64
 mg, 0.47 mmol) in 0.5 ml N,N-dimethylformamide. 1-Ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (100 mg, 0.52) was added and the solution was stirred for 20 min. Diisopropylethylamine (120 mg, 0.94 mmol) and N-methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (191 mg, 0.47 mmol) in 5 ml of dichloromethane was added
 5 and the mixture was allowed to stand overnight at room temperature. The mixture was washed with water (5 ml), sodium bicarbonate (5 ml) water (2 x 5 ml) and brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (20 g) with ethyl acetate as eluent to give 242 mg of (4-[N-Methyl-N-((1R)-1-(N-methyl-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]-carbamoyl]cyclohexyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): δ 1.0-1.8 (m, 8H) 1.5 (d, 9H) 2.4 (s, 3H) 2.7-3.3 (m, 4H) 2.9 (s, 3H) 3.0 (s, 3H) 3.7 (m, 1H) 4.6 (m, 1H) 5.2-5.8 (m, 2H) 7.0-7.8 (m, 12H)

15

4-Amino-cyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-carbamoyl]-2-(2-naphthyl)ethyl)amide:



20 To a solution of (4-[N-Methyl-N-((1R)-1-(N-methyl-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)-ethyl]carbamoyl]cyclohexyl)carbamic acid tert-butyl ester (240 mg, 0.38 mmol) in 1 ml dichloromethane was added 0.5 ml trifluoroacetic acid and the mixture was stirred for 5 min. Sodium bicarbonate was added until gas evolution has ceased, and the mixture was extracted with
 25 dichloromethane (3 x 15 ml). The combined organic phases were washed with

brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (16 g) with dichloromethane/methanol (4:1). The obtained product was dissolved in 3 ml of methanol and added 40 ml of water and 0.5 ml of acetic acid and lyophilized to give 99 mg of the title compound.

5

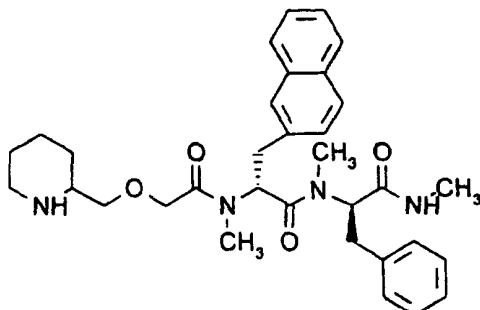
¹H-NMR (DMSO-d₆), (free base): d 1.2-1.5 (m, 8H) 2.05 (s, 3H) 2.65 (d, 3H) 2.7 (s, 3H) 2.5-3.3 (m, 6H) 5.4 (m, 1H) 5.6 (m, 1H) 7.1-7.8 (m, 12H)

HPLC: R_t = 30.2 min (method A1)

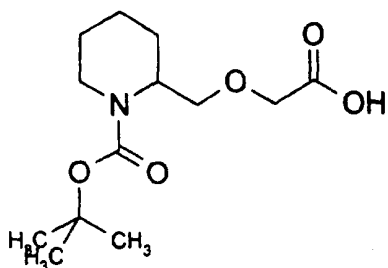
10

Example 29

N-Methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-2-(N-methyl-N-
15 {[(2-piperidinyloxy)methoxy]acetyl}amino)-3-(2-naphthyl)propinamide:



2-(Carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester:



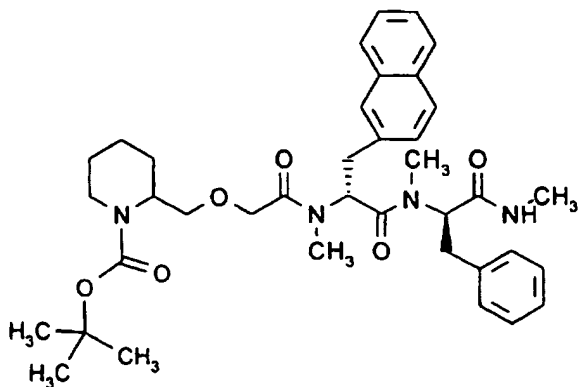
20

To a solution of N-(tert-butoxycarbonyl)-2-hydroxymethylpiperidine in 500 ml of dichloroethane was added 180 mg of rhodium(II)acetate and the mixture was

heated to 80 °C. Ethyldiazoacetate (3.7 ml, 35 mmol) in 180 ml dichloroethane was added (during approx. 1 hour) and stirred at 80°C for 6 hours. Another portion of ethyldiazoacetate (1.25 ml, 12 mmol) in 40 ml of dichloroethane was added (over 20 min) and the mixture was refluxed at 80°C for 7 h. The mixture was cooled to room temperature and washed with sodium bicarbonate (150 ml) and brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (100 g) with pentane:ethyl acetate (4:1) as eluent to give 2.64 g of 2-(((ethoxycarbonyl)methoxy)methyl)piperidine-1-carboxyl acid tert-butylester. The obtaining product was taken up in 40 ml of 1 M LiOH in water:methanol (1:3) and stirred at room temperature for 30 min. The mixture was concentrated in vacuo and water (20mL) was added and the solution was washed with ether (20mL). The aqueous phase was acidified to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (50 ml), dried over magnesium sulfate and concentrated in vacuo to give 2.41 g of 2-((carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester.

MHz-¹H-NMR (CDCl₃): d 1.45 (s, 9H) 1.55 (m, 2H) 1.85 (m, 2H) 3.1 (m, 2H) 3.6 (m, 1H) 3.8 (m, 2H) 4.15 (s, 2H)

2-([N-Methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]-carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl]methoxymethyl)piperidin-1-carboxylic acid tert-butyl ester:



To a solution of 2-(carboxymethoxymethyl)piperidine-1-carboxylic acid tert-butylester (225 mg, 0.82 mmol) in 5 ml of dichloromethane was added 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol) and 1-ethyl-3-(3-dimethylamino-
5 propyl)carbodiimide hydrochloride (173 mg, 0.90 mmol) and the mixture was to stirred for 30 min. N-Methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (332 mg, 0.82 mmol) in dichloromethane (5mL) was added followed by diisopropylethylamine (0.14 ml, 0.82 mmol) and the mixture was stirred overnight at room temperature. The mixture was washed with water (5 ml)
10 aqueous sodium bicarbonate (5 ml), water (2 x 5 ml), brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (20 g) with ethyl acetate to give 416 mg of 2-([N-methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl]methoxymethyl)piperidin-1-carboxylic acid tert-butyl ester.

15

¹H-NMR (CDCl₃) (selected peaks): d 1.45 (s, 9H) 2.45 (d, 3H) 2.75 (d, 3H) 2.90 (d, 3H) 3.0 (s, 2H)

20 To a solution of 2-([N-methyl-N-((1R)-1-(N-methyl-N-[(1R)-1-(methylcarbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl]methoxymethyl)piperidin-1-carboxylic acid tert-butyl ester (388 mg, 0.60 mmol) in dichloromethane (1mL) was added trifluoroacetic acid (1mL) and the mixture was stirred for 10 min at room temperature. Then saturated sodium bicarbonate was added until pH 8 and the
25 organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (15 g) with dichloromethane:methanol (9:1) to give 273 mg of the title compound.

30

¹H-NMR (CDCl₃) (selected peaks): d 5.3 (m, 1H) 5.75 (t, 1H) 7.0-7.8 (m, 12H)

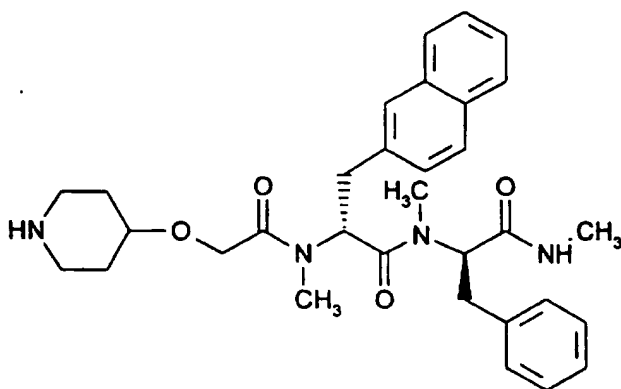
EI/SPMS : 559.5 (M+)

HPLC: R_t = 32.0 (Method A1)

5

Example 30

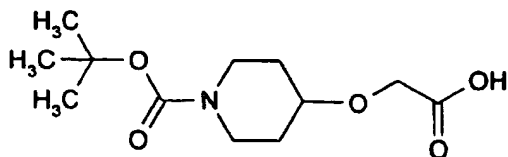
(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(methyl[4-ploxy]acetyl]amino)-3-(2-naphthyl)propionamide:



10

4-(Carboxymethoxy)piperidine-1-carboxylic acid tert-butyl ester:

15



To a solution of 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (5.0 g, 25 mmol) and rhodium(II)acetate (180 mg) in 500 ml dichloroethane at 80°C was added (over 90 min) ethyl diazoacetate (4.2 ml, 50 mmol) in 220 ml dichloroethane. The mixture was stirred for 7 h and quenched with aqueous sodium bicarbonate (2 x 100 ml). The organic phase was isolated and washed with brine (2 x 100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (80g) in petroleum ether:ethyl acetate (4:1) to give 3.4 g

of 4-(ethoxycarbonylmethoxy)piperidine-1-carboxylic acid tert-butylester. The product was taken up in 40 ml of a 1 M lithium hydroxide solution in water:methanol (1:3) and stirred for 60 min. The mixture was concentrated in vacuo and dissolved in 20 ml of water, acidified to pH 4 with 1 M aqueous hydrogen chloride and
5 extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine (10 ml), dried over magnesium sulfate and concentrated in vacuo to give 1.79 g of 4-(carboxymethoxy)piperidine-1-carboxylic acid tert-butyl ester.

¹H-NMR (CDCl₃): d 1.45 (s, 9H) 1.55 (m, 2H) 1.9 (m, 2H) 3.1 (m, 2H) 3.6 (m, 1H)
10 3.8 (m, 2H) 4.2 (s, 2H)

A solution of 4-(carboxymethoxy)piperidine-1-carboxylic acid tert-butyl ester (228
15 mg, 0.88 mmol), 1-hydroxy-7-azabenzotriazole (120 mg, 0.88 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (186 mg, 0.97 mmol) was stirred for 30 min at room temperature. N-Methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(naphthalen-2-yl)propionamide (355 mg, 0.88 mmol) in 5 ml of dichloromethane was added followed by diisopropylethylamine (0.2
20 ml, 1.14 mmol) and the mixture was stirred for 2 days at room temperature. The mixture was washed with water (5 ml) aqueous sodium bicarbonate (5 ml), water (2 x 5 ml), brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (30 g) with ethyl acetate as eluent to give 391 mg of 4-([N-methyl-N-[(1R)-1-(N-methyl-N-[(1R)-1-(methyl carbamoyl)-2-phenylethyl]carbamoyl)-2-(2-naphthyl)ethyl]carbamoyl]methoxy]piperidin-1-
25 carboxylic acid tert-butylester. The product was taken up in 50% trifluoromethane/dichloromethane and allowed to stand for 10 min. Then saturated sodium bicarbonate was added until pH was about 8 and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and
30 the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (15 g) with dichloromethane:methanol (9:1) to give 327 mg of the title compound.

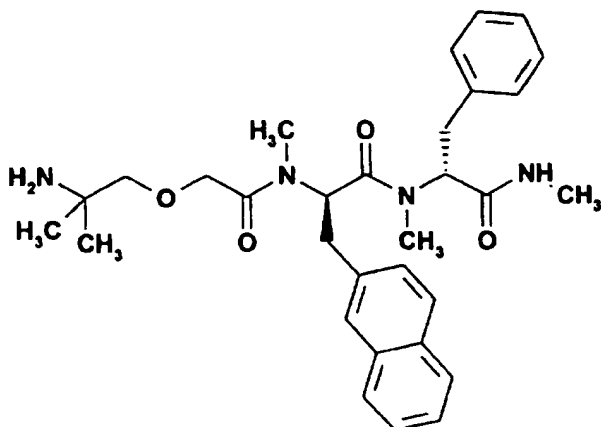
¹H-NMR (CDCl₃) (selected peaks): d 3.75 (q, 2H) 5.5 (m, 1H) 5.8 (t, 1H) 7.0-7.8 (m, 12H)

5 EI/SPMS: 544.5 (M⁺)

HPLC: R_t = 28.9 (Method A1)

10 Example 31

2-[1-Methyl-2-(2-amino-(2-methylpropoxy))acetylamino]-N-(1-methyl-1-((1-methylcarbamoyl)-2-(2-phenylethyl)-3-(2-naphthyl))propionamide:



15

A solution of 2-t-butoxycarbonylamino-2-methylpropanol (5.0 g, 26.46 mmol) and rhodium(II)acetate (90 mg) in dichloroethane (500 mL) was heated to 80 °C.

Ethyldiazoacetate (4.0 g, 34.78 mmol) was slowly added over a period of 1 hr.,

20 and the mixture was stirred at reflux for 3 hr. Another 90 mg of rhodium(II)acetate was added and the mixture was refluxed for another 5 hr. The mixture was cooled overnight and 500 ml of saturated sodium bicarbonate was added, the yellow organic layer was separated and washed twice with saturated sodium bicarbonate (2 x 200 ml). The organic layer was dried over magnesium sulfate and

25 concentrated in vacuo. The yellow oil was taken up in 200 ml of 1 M Lithium

hydroxide in methanol:water (3:1) and stirred overnight. The solvent was removed in vacuo to a minimum and water was added (pH>9) and the mixture was washed with ether. Then 1 M hydrogen chloride was added until pH<4 and the mixture was extracted with ethyl acetate, dried over magnesium sulfate and concentrated in vacuo to give 2.5 g (38%) of (2-t-butoxycarbonylamino-2-methylpropoxy) acetic acid as a clear oil.

^1H -NMR (CDCl_3 , 400 MHz) δ 1.3 (s, 6H); 1.45 (s, 9H); 3.5 (s, 2H); 4.15 (s, 2H); 9.9 (b, 1H).

10

A solution of (2-tert-butoxycarbonylamino-2-methylpropoxy) acetic acid (184 mg, 0.74 mmol), 1-hydroxy-7-azobenzotriazole (101 mg, 0.74 mmol) and 1-ethyl-3-dimethylaminopropyl carbodiimide hydrochloric acid (157 mg, 0.82 mmol) in 9 ml of methylene chloride and 1 ml of DMF was stirred for 15 min. Then N-methyl-2-methylamino-N-(1-methylcarbamoyl-2-phenylethyl)-3-(naphthalen-2-yl)propionamide (300 mg, 0.74 mmol) and diisopropylethylamine (96 mg, 0.74 mmol) in 1 ml of methylene chloride were added and allowed to stir overnight. The mixture was washed with saturated sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo. The mixture was chromatographed on 100 ml of silica gel with ethyl acetate to give 360 mg (76 %) of 2-[1-methyl-2-(2-(t-butoxycarbonyl)amino-(2-methylpropoxy))acetylaminol-N-(1-methyl-1-((1-methylcarbamoyl)-2-(2-phenylethyl)-3-(2-naphthyl))propionamide. The obtained mixture was taken up in 1 ml of TFA and 1 ml of methylene chloride and stirred at 0°C for 5 min. Then saturated sodium bicarbonate was slowly added to the cooled solution and the organic layer was separated, washed with sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo to give 185 mg (47% from (2-t-butoxycarbonylamino-2-methylpropoxy) acetic acid) of 2-[1-methyl-2-(2-amino-(2-methylpropoxy))acetylaminol-N-(1-methyl-1-((1-methylcarbamoyl)-2-(2-phenylethyl)-3-(2-naphthyl))propionamide as an oil. The obtained oil was dissolved in 0.1 N acetic acid (50 ml) and lyophilized to give an amorph white powder.

^1H -NMR (CDCl_3 , 400 MHz, free amine) δ 0.9 (d, 3H); 1.05 (d, 3H); 2.35 (s, 3H); 2.75 (s, 3H); 2.8 (s, 3H); 2.9 (s, 2H); 3.0 (s, 2H); 3.0-2.7 (m, 2 H); 3.25 (m, 2H); 3.7 (t, 1H); 5.1 (dd, $J=20$ Hz, 1H); 5.8 (t, 1H, amine); 7.8-6.9 (m, 12H).

5

HPLC: R_t = 30.65 min in A1; 97 % purity

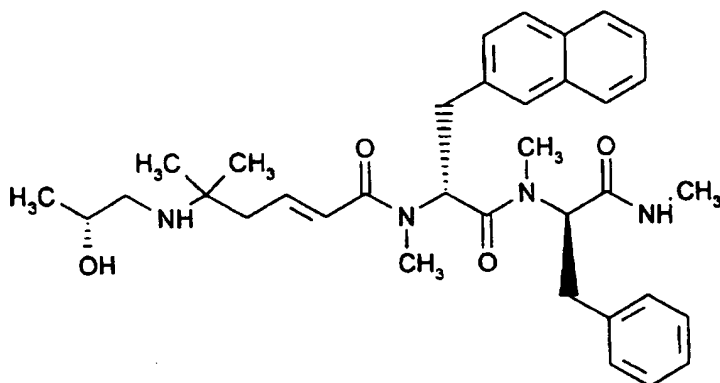
Calculated for $\text{C}_{31}\text{H}_{40}\text{N}_4\text{O}_4$, CH_3COOH , H_2O :

C, 64.9 %; H, 7.6 %; N, 9.1 %; Found:

10 C, 64.2 %; H, 7.6 %; N, 8.5 %

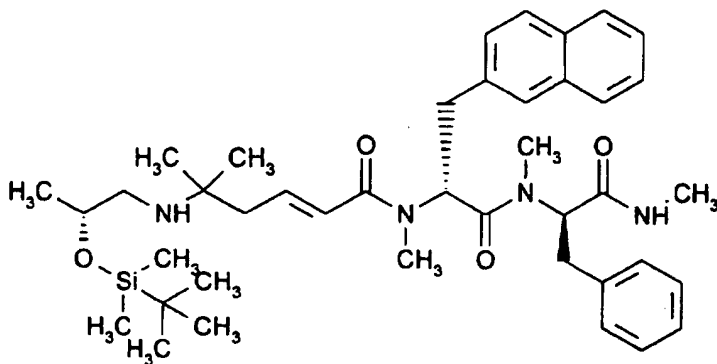
Example 32

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-Hydroxypropylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;



20

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-(tert-Butyldimethylsilyloxy)propylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;



5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide (318 mg, 0.60 mmol) was dissolved in methanol (20 ml) and glacial acetic acid (0.48 ml, 8.4 mmol). 3 Å mol sieves (9 g) and a solution of (2R)-2-(tert-

- 10 butyldimethylsilyloxy)propanal (1.33 g, 7.06 mmol) in methanol (10 ml) were added successively. Sodium cyanoborohydride (220 mg, 3.53 mmol) was added as a solid. The reaction mixture was stirred at room temperature for 45 min, before a second batch of sodium cyanoborohydride (220 mg, 3.53 mmol) was added. The reaction mixture was stirred for 16 h at room temperature. The mol sieves was
- 15 filtered off through a plug of celite. The celite was washed with methanol (200 ml). The solvents of the combined filtrates were removed in vacuo. The residue was dissolved in 1 N sodium hydroxide solution (50 ml) and tert-butyl methyl ether (50 ml). The phases were separated. The aqueous phase was extracted with tert-butyl methyl ether (3 x 50 ml). The combined organic layers were dried over magnesium
- 20 sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (35 g), using ethyl acetate/heptane/triethylamine (20:10:1) as eluent, to give 99 mg of (2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-(tert-butylidimethylsilyloxy)propylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide.

25

¹H-NMR (CDCl₃, selected values): d 0.04, 0.05, and 0.10 (all s, together 6 H); 0.85 and 0.91 (both s, together 9 H); 3.86 (m, 1 H); 6.04 and 6.08 (both d, together 1 H); 6.89 (m, 1 H).

5 MS: 701.2 [M+1].

HPLC: The RP-analysis was performed using UV detections at 214, 254, 276, and 301 nm on a 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1 mL/min at 42°C. The column was
10 equilibrated with 5% acetonitrile in a buffer consisting of 0.1% aqueous trifluoro acetic acid eluted by a gradient of 0% to 90% of 0.1% trifluoro acetic acid in acetonitrile during 50 min: R_t = 37.25 min.

15

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-(tert-Butyldimethylsilyloxy)propylamino)-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide (99 mg, 0.14 mmol) was dissolved in tetrahydrofuran (2 ml). Tetra-n-butylammonium fluoride (0.18 ml of a 1.1 M solution in
20 tetrahydrofuran, 0.2 mmol) was added. The solution was stirred for 3 h, before another portion of tetra-n-butylammonium fluoride (0.23 ml of a 1.1 M solution in tetrahydrofuran, 0.25 mmol) was added. The reaction mixture was stirred for 2.5 h at room temperature and diluted with ethyl acetate (50 ml). It was extracted with 10% sodium carbonate solution (30 ml). The aqueous phase was extracted with
25 ethyl acetate (20 ml). The organic layers were combined and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash-chromatography on silica (30 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 28 mg of the title compound.

30 ¹H-NMR (CDCl₃, selected values): d 3.65 and 3.72 (both m, together 1 H); 5.15 and 5.30 (both dd, together 1 H); 5.60 and 5.90 (both dd, together 1 H); 6.03 and 6.05 (both d, together 1 H); 6.78 (m, 1 H).

MS: 587.2 [M+1].

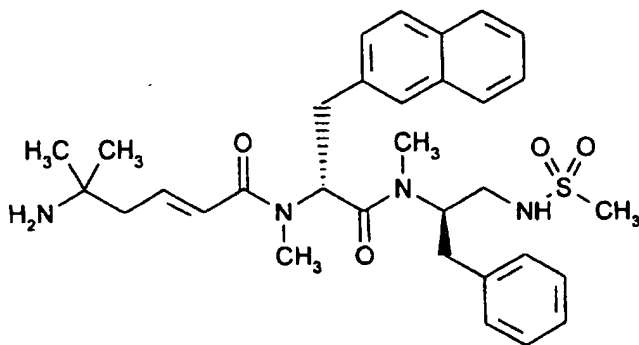
HPLC: $R_t = 27.47$ (A1).

5 $R_t = 27.12$ (B1).

For biological testing it was transferred into the acetate by liophilization from 0.5 M
10 acetic acid (20 ml).

Example 33

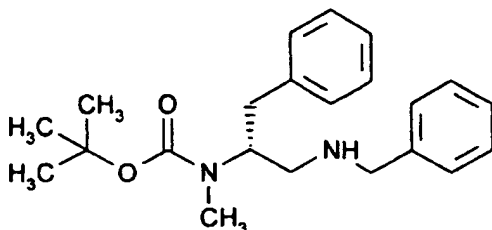
(2E)-5-Amino-N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-
15 methylcarbamoyl)-2-(2-naphthyl)ethyl)-5-methyl-N-methylhex-2-enamide;



20

N-((1R)-1-Benzyl-2-(benzylamino)ethyl)-N-methylcarbamic acid tert-butylester;

25



5 A solution of oxalyl chloride (3.16 ml, 36.17 mmol) in dichloromethane (50 ml) was cooled to -78 °C. A solution of dimethylsulfoxide (3.42 ml, 48.22 mmol) in dichloromethane (50 ml) was added dropwise. The reaction mixture was stirred for 5 min at -78 °C. A solution of N-((1R)-1-(hydroxymethyl)-2-phenylethyl)-N-methylcarbamate tert-butylester (6.40 g, 24.11 mmol) in dichloromethane (100
10 ml) was added dropwise over a period of 10 min. The solution was stirred for 25 min at -78 °C. Ethyldiisopropylamine (16.68 ml, 96.44 mmol) was added dropwise at -78 °C. The solution was warmed to -35 °C, and immediately cooled to -78 °C. Glacial acetic acid (6.07 ml, 106.08 mmol) was added. The reaction mixture was warmed to room temperature and diluted with dichloromethane (150 ml). It was
15 washed with saturated sodium chloride solution (2 x 200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was dissolved in methanol (200 ml). Benzylamine (2.6 ml, 24.1 mmol) was added. Glacial acetic acid (6.0 ml, 106 mmol) and 3 Å mol sieves (32 g) were added. Sodium cyanoborohydride (1.00 g, 15.9 mmol) was added as a solid. The reaction
20 mixture was stirred for 1h, before another portion of sodium cyanoborohydride (0.97 g, 15.4 mmol) was added. The mixture was first stirred for 16 h at room temperature and successively left 3 days without stirring. The mol sieves was filtered off through a plug of celite. The celite was washed with methanol (200 ml). The solvent was removed in vacuo. The residue was dissolved in 1 N sodium hydroxide
25 solution/diethyl ether (250 ml/250 ml). The phases were separated. The aqueous phase was extracted with diethyl ether (2 x 100 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (230 g), using

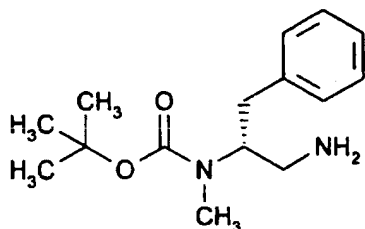
dichloromethane/methanol/25% aqueous ammonia (first 100:10:1, then 50:10:1) as eluent, to give 4.54 g of N-((1R)-1-benzyl-2-(benzylamino)ethyl)-N-methylcarbamic acid tert-butylester.

5 ¹H-NMR (CDCl₃): d 1.28 and 1.36 (both br, together 9 H); 2.50 - 2.90 (m, 8 H); 3.70 (d, 1 H); 3.88 (d, 1 H); 4.45 and 4.65 (both br, together 1 H); 7.10 - 7.40 (m, 10 H).

MS: 355.2 [M+H]⁺.

10

N-((1R)-1-Aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester;



15

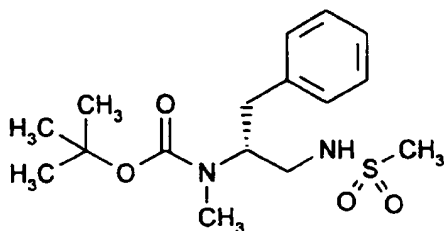
A suspension of 20% palladium hydroxide on charcoal (4.63 g) and N-((1R)-1-benzyl-2-(benzylamino)ethyl)-N-methylcarbamic acid tert-butylester (4.40 g, 12.4 mmol) was kept for 8 h under a hydrogen atmosphere at (pressure: 1 atm). The reaction mixture was flushed with nitrogen and filtered through a plug of celite. The solvent was removed. The crude product was purified by flash chromatography on silica (110 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 830 mg of N-((1R)-1-aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

25

¹H-NMR (CDCl₃): d 1.29 and 1.36 (both s, together 9 H); 1.40 (s, 2 H); 2.60 - 2.90 (m, 7 H); 4.20 and 4.38 (both br, together 1 H); 7.10 - 7.35 (m, 5 H).

N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamic acid tert-butylester;

5



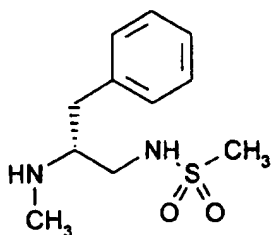
N-((1R)-1-Aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester (830
10 mg, 3.14 mmol) was dissolved in dichloromethane (15 ml). Triethylamine (0.44 ml,
3.14 mmol) was added. The solution was cooled to -78 °C. A solution of
methanesulfonyl chloride (0.24 ml, 3.14 mmol) in dichloromethane (2 ml) was
added dropwise. The reaction mixture was stirred for 16 h, while it was warming up
to room temperature. It was diluted with dichloromethane (100 ml) and washed with
15 saturated sodium chloride solution (100 ml). It was dried over magnesium sulfate.
The solvent was removed in vacuo. The crude product was purified by flash
chromatography on silica (65 g), using ethyl acetate/heptane (2:1) as eluent, to give
990 mg of N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamic acid
tert-butylester.

20

¹H-NMR (CDCl₃): δ 1.30 and 1.40 (both br, together 9 H); 2.60 - 3.00 (m, 5 H); 2.93
(br, 3 H); 3.15 - 3.50 (m, 2 H); 4.40 (br, 1 H); 4.50 and 4.70 (both br, together 1 H);
7.05 - 7.35 (m, 5 H).

25

N-((2R)-2-Methylamino-3-phenylpropyl)methansulfonamide;

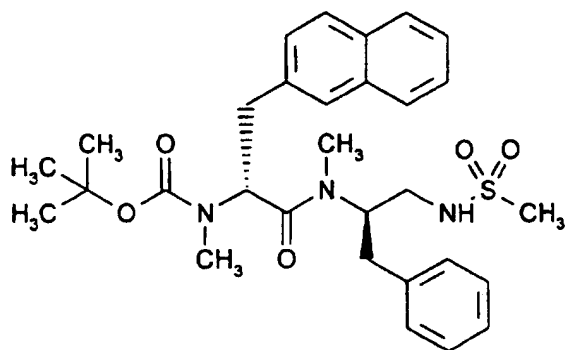


At 0 °C, trifluoroacetic acid (5 ml) was added to a solution of N-((1R)-1-benzyl-2-
 ((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl-2-phenylpropylmethansulfonamide (913 mg, 2.67
 5 mmol) in dichloromethane (5 ml). The reaction mixture was stirred for 15 min at 0
 °C. The solvent was removed in vacuo without warming. The residue was dissolved
 in dichloromethane (50 ml) and the solvent was removed in vacuo. The latter
 procedure was repeated two times. The crude product was purified by flash
 chromatography on silica (20 g), using dichloromethane/methanol/25% aqueous
 10 ammonia as eluent, to give 658 mg of N-((2R)-2-methylamino-3-phenylpropyl)methansulfonamide.

¹H-NMR (CDCl₃, selected values): d 2.39 (s, 3 H); 2.70 - 3.00 (m, 4 H); 2.95 (s, 3
 H); 3.22 (dd, 1 H), 7.15 - 7.35 (m, 5 H).

15

N-((1R)-1-(N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-
 (2-naphthyl)ethyl)-N-methylcarbamoyl-2-phenylpropylmethansulfonamide;

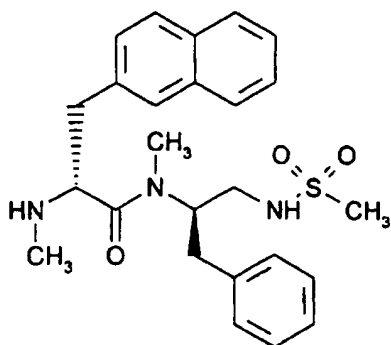


20

(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (1.05 g, 3.2 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). Hydroxy-7-azabenzotriazole (434 mg, 3.2 mmol) was added as a solid. The
5 solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (612 mg, 3.2 mmol) was added. The solution was stirred for 5 min at 0 °C. A solution of N-((2R)-2-methylamino-3-phenylpropyl)methanesulfonamide (703 mg, 2.9 mmol) in dichloromethane (2 ml) was added. Ethyldiisopropylamine (0.50 ml, 2.90 mmol) was added. The solution was stirred for 27 h, while it was warming
10 up to room temperature. It was diluted with ethyl acetate (200 ml) and extracted with 1 N hydrochloric acid (100 ml). The aqueous phase was extracted with ethyl acetate (50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on
15 silica (45 g), using ethyl acetate/heptane (2:1) as eluent, to give 1.037 g of N-((1R)-1-(N-((1R)-1-Benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃, selected values): d 1.30 and 1.34 (both br, together 9 H); 7.00 -
20 7.90 (m, 12 H).

N-((2R)-2-(N-Methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropyl)methanesulfonamide;



At 0 °C, trifluoroacetic acid (4 ml) was added to a solution of N-((1R)-1-(N-((1R)-1-
 5 benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-
 methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butylester (997 mg, 1.8 mmol) in dichloromethane (4 ml).
 The solution was stirred for 15 min at 0 °C. The solvent was removed in vacuo at 20
 °C. The residue was dissolved in dichloromethane and the solvent was removed in
 vacuo. The latter procedure was repeated two times. The crude product was
 10 purified by flash chromatography on silica (45 g), using
 dichloromethane/methanol/25% aqueous ammonia as eluent, to give 646 mg of N-
 ((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-
 phenylpropyl)methanesulfonamide.

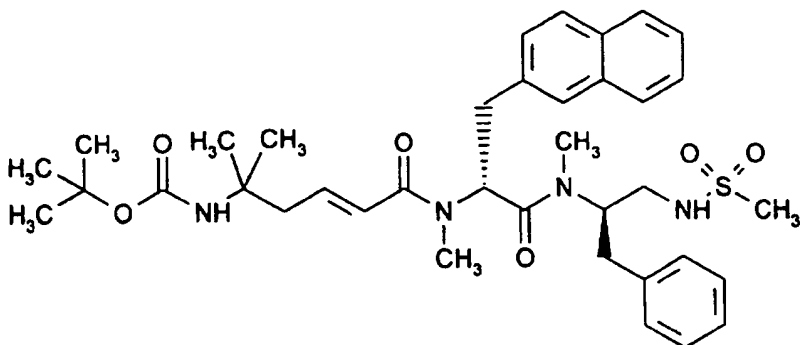
15 ¹H-NMR (CDCl₃, selected values): d 1.87, 2.33, 2.38, 2.50, 2.62, 2.80, 2.82, 2.88,
 and 2.92 (all s, together 9 H); 3.62 and 3.76 (both dd, together 1 H); 4.56 and 4.72
 (both br, together 1 H); 4.84 and 5.02 (both br, together 1 H); 6.90 - 7.95 (m, 12 H).

MS: 454.2 [M+H]⁺.

20

(3E)-4-(N-((1R)-1-(N-((1R)-1-Benzyl-2-(methylsulfonylamino)ethyl)-N-
 methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-
 enylcarbamic acid tert-butyl ester;

25



5 (2E)-5-tert-Butoxycarbonylamino-5-methylhex-2-enoic acid (352 mg, 1.45 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). Hydroxy-7-azabenzotriazole (197 mg, 1.45 mmol) was added as a solid. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (278 mg, 1.45 mmol) was added. The solution was stirred for 15 min

10 at 0 °C. A solution of N-((2R)-2-(N-methyl-N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)amino)-3-phenylpropyl)methanesulfonamide (598 mg, 1.32 mmol) in dichloromethane (2 ml) and ethyldiisopropylamine (0.23 ml, 1.32 mmol) were added successively. The solution was stirred for 18 h, while it was warming up to room temperature. It was diluted with ethyl acetate (100 ml) and extracted with 1

15 N hydrochloric acid. The aqueous phase was extracted with ethyl acetate (50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (60 g), using ethyl acetate/heptane (2:1) as eluent to give 740 mg of (3E)-4-

20 (N-((1R)-1-(N-((1R)-1-benzyl-2-(methylsulfonylamino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values): d 2.60, 2.80, 2.89, 2.92, 3.06, and 3.17 (all s, together 9 H); 6.06 and 6.25 (both d, together 1 H); 6.82 and 6.96 (both m, together

25

1 H); 7.00 - 7.85 (m, 12 H).

(3E)-4-(N-((1R)-1-(N-((1R)-1-Benzyl-2-(methylsulfonylamino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butyl ester (729 mg, 1.07 mmol) was dissolved in dichloromethane (3 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (3 ml) was added. The reaction mixture was stirred for 15 min at 0 °C. The solvents were removed in vacuo at 20 °C. The residue was dissolved in dichloromethane (100 ml) and the solvent was removed in vacuo. The latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (60 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 440 mg of the title compound as free base.

¹H-NMR (CDCl₃, selected values): d 1.10, 1.11, 1.14, and 1.15 (all s, together 6 H); 2.64, 2.71, 2.88, 2.90, 3.06, 3.18 (all s, together 9 H); 4.76 and 5.00 (both br, together 1 H); 4.95 and 5.09 (both dd, together 1 H); 6.08 and 6.28 (both d, together 1 H); 6.83 and 7.00 (both m, together 1 H).

MS: 579.0 [M+H]⁺.

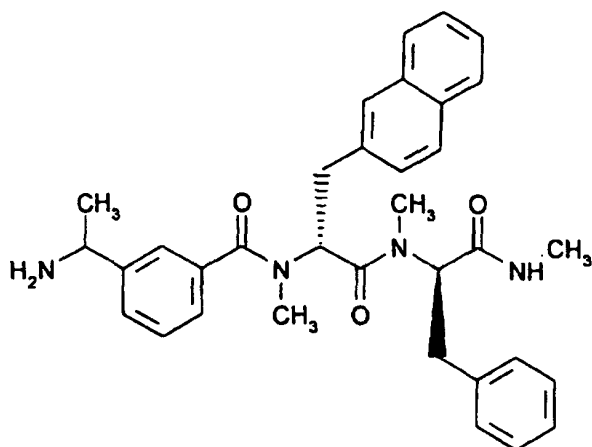
HPLC: R_t = 31.98 min (A1).

R_t = 27.53 min (B1).

For biological testing the title compound was transferred into its acetate by lyophilization from 40 ml 0.5 M aqueous acetic acid.

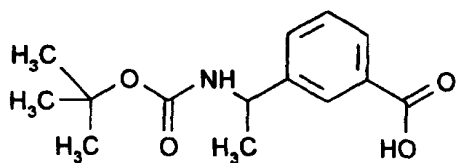
Example 34

3-(1-Aminoethyl)benzoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide:



5

3-(1-(N-tertbutoxycarbonyl)aminoethyl)benzoic acid:



- Ammonium acetate (10.6 g, 138 mmol) was evaporated from dry ethanol
 10 (100 mL), and redissolved in dry methanol (100 mL) over molecular sieves
 (3Å, 3 g). 3-Acetylbenzonitrile (2.0 g, 13.8 mmol) was added. After 30
 minutes at room temperature sodium cyanoborohydride (0.87 g, 138 mmol)
 was added and the reaction mixture was stirred for 18 hours. The reaction
 mixture was concentrated in vacuo and redissolved in water (100 mL).
 15 Concentrated hydrochloric acid was added until pH 2, and the aqueous
 solution was extracted with ethyl acetate (2 x 100 mL). The aqueous phase
 was adjusted to pH 11 with solid potassium hydroxide, and extracted with
 dichloromethane (2 x 100 mL). The combined organic phases were dried
 (magnesium sulfate) and concentrated in vacuo. A concentrated solution of
 20 hydrogen chloride in ethyl acetate added (100 mL) was, and the solution
 was concentrated in vacuo. The residue was dissolved in ethanol (25 mL)

- and sulphuric acid (9N, 25 mL) was added. After 16 hours at room temperature and 2 hours at reflux temperature the ethanol was removed by evaporation in vacuo and the residual aqueous mixture was adjusted to pH > 8 using solid potassium hydroxide. Ditertbutyldicarbonate (2.0 g) dissolved
- 5 in tetrahydrofuran (100 mL) was added at 0°C. After 18 hours at room temperature the reaction mixture was concentrated in vacuo and redissolved in water (100 mL). Solid citric acid was added until pH 5. The reaction mixture was extracted with dichloromethane (2 x 100 mL), and the combined organic phases was dried (magnesium sulfate) and concentrated in vacuo.
- 10 The residue was purified by column chromatography on silica gel (3 x 40 cm) using ethanol and dichloromethane (1:9) as eluent to give 1.1 g of 3-(1-(N-tert-butoxycarbonyl)aminoethyl)benzoic acid.
- 15 3-(1-(N-tert-Butyloxycarbonyl)aminoethyl)benzoic acid (132 mg, 0.50 mmol), 1-hydroxy-7-azabenzotriazole (68 mg, 0.50 mmol) and 1-ethyl-3(3-dimethylaminopropyl)carbodiimide hydrochloride (96 mg, 0.50 mmol) were dissolved in N,N-dimethylformamide (3 mL) and stirred for 15 min.
- (2R)-N-Methyl-N-((1R)-2-phenyl)-1-(methylcarbonyl)ethyl)-2-methylamino-
- 20 3-(2-naphthyl)propionamide (100 mg, 0.25 mmol) dissolved in dichloromethane (6 mL) was added followed by addition of diisopropylethylamine (0.085 mL, 0.50 mmol) and the mixture was stirred for 20 hours.
- The reaction mixture was evaporated in a stream of nitrogen and the residue
- 25 was dissolved in ethyl acetate (25 mL). The mixture was washed with aqueous sodium hydrogen carbonate (2 x 25 mL, 5%) and aqueous potassium hydrogen sulfate (25 mL, 5%). The organic phase was dried (sodium sulfate) and evaporated in vacuo. The residue was dissolved in dichloromethane (2.5 mL), cooled to 0-4° C and treated with trifluoroacetic
- 30 acid (2.5 mL) for 10 minutes at 0-4° C. The volatiles were removed with a stream of nitrogen and the oily residue was dissolved in 0.1 % trifluoroacetic acid in acetonitrile and water (7:3, 10 mL) and diluted with water (290 mL).

This solution was submitted to semipreparative HPLC purification using a 25x200 mm C18 column and using a linear gradient of 25-40% acetonitrile in water containing 0.1M ammonium sulfate (pH 2.5). The product was purified in three runs and after ion exchange on a Waters Seppak C18 the
5 effluent was lyophilised to give the title compound.

PD-MS: Calculated 551.7 (M+1); Found 551.3 (M+1)

HPLC: Rt = 31.8 min (Method A1)

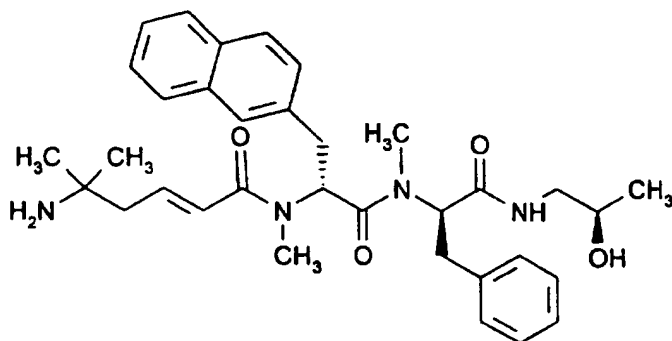
Rt = 33.93 min (Method B1)

10

Example 35

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2R)-
2-hydroxypropylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)

15 methylamide:



20 The title compound was prepared analogously to example 1.

¹H-NMR (CDCl₃): (selected peaks for major rotamer) δ 1.09 (d, 3H); 1.19 (s, 6H);
2.97 (s, 3H); 2.99 (s, 3H); 5.15 (dd, 1H); 5.53 (dd, 1H); 6.12 (d, 1H)

25 HPLC : t_r = 31.8 min. (A1)

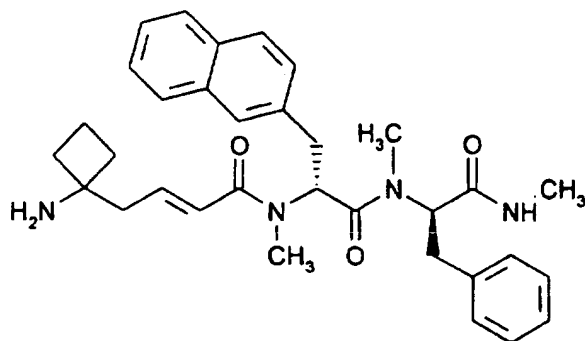
PDMS : m/z 573.7 (M+H)⁺

5 Example 36

(4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-(((1R)-1-(1-methylcarbamoyl-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamid

e:

10



The title compound was prepared analogously to example 1. (4-
15 (1-Aminocyclobutyl)but-2-enoic acid was prepared as in R. Graf, Org. Synth. 46,
51 (1966) and example 1.

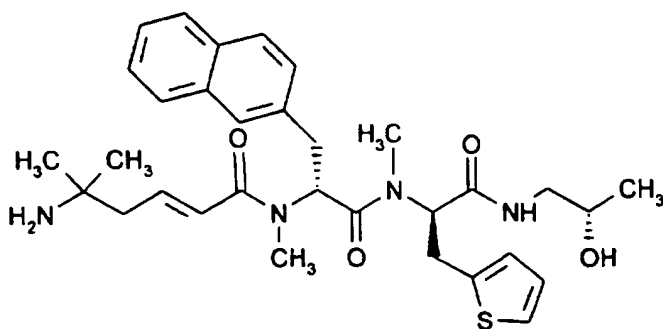
¹H-NMR (CDCl₃): (selected peaks for major rotamer) δ 2.26 (s, 3H); 2.98 (s, 3H);
3.00 (s, 3H); 5.15 (dd, 1H); 5.57 (dd, 1H); 6.11 (d, 1H).

20

HPLC : t_r = 32.2 min. (A1)

Example 37

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-
 5 2-hydroxypropylcarbamoyl)-2-(2-
 thienyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.



10

This compound was prepared analogously to example 1.

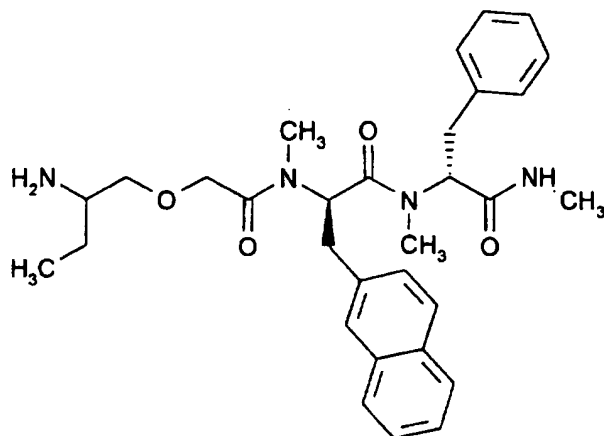
¹H-NMR (CDCl₃): (selected peaks for major rotamer) δ 1.10 (d, 3H); 1.14 (s, 3H);
 1.15 (s, 3H); 2.18 (d, 2H); 2.95 (s, 3H); 3.05 (s, 3H); 5.28 (dd, 1H); 5.72 (dd, 1H);
 15 6.07 (d, 1H).

HPLC : t_r = 30.4 min. (A1)

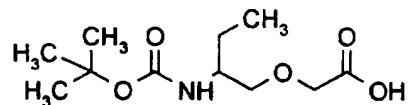
Example 38

20

(2R)-2-(N-[(2R)-2-(N-[(2-Aminobutoxy)acetyl]-N-methylamino)-3-
 (2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide:



(2-(tert-Butoxycarbonylamino)butoxy)acetic acid :



- 5 To a solution of (1-(hydroxymethyl)propyl)carbamic acid tert-butylester (7.2 g, 39 mmol) in 1,2-dichloroethane (500 ml) rhodium(II)acetate (180 mg) was added and the mixture was heated to 80 °C. Ethyldiazoacetate (6.0 ml, 57 mmol) in 1,2-dichloroethane (180 ml) was added over a period of 60 min and the mixture was
- 10 heated at 80 °C for 6 hours. Then another portion of ethyldiazoacetate (2.0 ml, 19 mmol) in 1,2-dichloroethane (40 ml) was added and the mixture was refluxed for 7 hours. The mixture was cooled to room temperature and washed with sodium bicarbonate (2 x 100 ml) and brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (300 g)
- 15 with pentane/ethyl acetate 7:3 as eluent to give 4.3 g of (2-(tert-butoxycarbonylamino)butoxy)acetic acid ethylester. The product was dissolved in of 1 M lithium hydroxide in water/methanol 1:3 (40 ml) and stirred at room temperature for 4 hours. The mixture was concentrated in vacuo and water (100 mL) was added and the solution was washed with ether (20 mL). The aqueous phase was acidified
- 20 to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (200 ml), dried over magnesium sulfate and concentrated in vacuo to give 2.46 g of (2-(tert butoxycarbonylamino)butoxy)acetic acid.

¹H-NMR (CDCl₃): δ 0.95 (t, 3H) 1.45 (s, 9H) 1.60 (m, 3H) 3.55 (m, 2H) 4.10 (s, 2H)

5 To a solution of (2-(tert-butoxycarbonylamino)butoxy)acetic acid (1.1 g, 4.5 mmol) in dichloromethane (20 ml) were added 1-hydroxy-7-azabenzotriazole (612 mg, 4.5 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (9.5 mg, 5.0 mmol) and the mixture was stirred for 30 min. (2R)-N-methyl-2-methylamino-N-((1R)-1-methyl-carbamoyl-2-phenylethyl)-3-(2-naphthyl)propionamide (605 mg, 1.5
10 mmol) in dichloromethane (10 ml) was added followed by diisopropylethylamine (0.33 ml, 2.0 mmol) and the mixture was stirred for 2 hours at room temperature. The mixture was washed with water (10 ml), saturated aqueous sodium bicarbonate (10 ml), water (2 x 10 ml), brine (10 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (40
15 g) with ethyl acetate/heptane 4:1 to give 766 mg of (1-[[N-methyl-N-((1R)-1-[N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl]-2-(2-naphthyl)ethyl)carbamoyl]methoxymethyl]-propyl)carbamic acid tert-butylester. The obtained product was taken up in 50% trifluoroacetic acid in dichloromethane (5 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8
20 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo to give (2R)-2-(N-[(2R)-2-(N-[[2-aminobutoxy]acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide as an oil. The product was
25 redissolved in water (30 ml) and acetic acid (2 ml) was added and the mixture was lyophilized to give 645 mg of the acetate salt of the title compound as an amorphous powder.

LC-MS : 533.0 (M+H)⁺

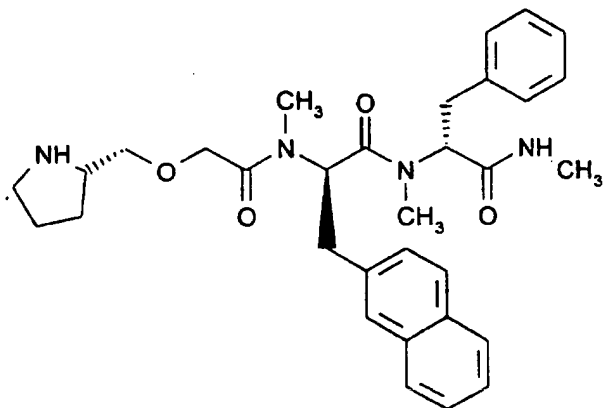
30 HPLC: R_t = 31.1 (Method A1)

¹H-NMR (DMSO) (selected peaks): d 0.6-0.8 (m, 3H) 2.65 (d, 3H) 2.75 (s, 3H) 5.35 (dd, 1H) 5.65 (dd, 1H) 7.1-7.9 (arom, 12H)

Example 39

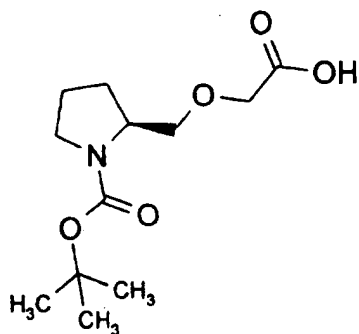
5

(2R)-N-Methyl-2-(N-methyl-N-((2R)-2-(N-methyl-N-(((2S)-pyrrolidin-2-yl)methoxy)acetyl)amino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionamide



10

(2S)-2-(((Carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester



To a solution of N-t-butyloxycarbonyl-(S)-prolinol (5.0 g, 25 mmol) in 1,2-dichloroethane (500 ml) rhodium(II)acetate (180 mg) was added and the mixture
 15 was heated to 80 °C. Ethyldiazoacetate (3.9 ml, 37 mmol) in 1,2-dichloroethane (180 ml) was added over a period of 90 min and the mixture was heated at 80 °C for 3 hours. Then another portion of ethyldiazoacetate (1.3 ml, 12 mmol) in 1,2-dichloroethane (40 ml) was added and the mixture was refluxed for 6 hours. The mixture was cooled to room temperature and washed with saturated sodium

bicarbonate (2 x 100 ml) and brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (300 g) with petrol ether/ethyl acetate 4:1 as eluent to give 4.7 g of (2S)-2-(((ethoxycarbonyl)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester. The
5 obtained product was taken up in 50 ml of 1 M lithium hydroxide in water/methanol 1:3 and stirred at room temperature overnight. The mixture was concentrated in vacuo, water (20 mL) was added and washed with ether (20 mL). The aqueous phase was acidified to pH 4 with 1 M aqueous hydrogen chloride and extracted with ethyl acetate (200 ml), dried over magnesium sulfate and concentrated in vacuo to
10 give 3.6 g of (2S)-2-(((carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butylester.

¹H-NMR (CDCl₃): δ 1.45 (2, 9H) 1.90 (m, 4H) 3.55 (t, 2H) 3.60 (m, 3H) 4.10 (s, 2H) 10.6 (s, 1H)

15

To a solution of (2S)-2-(((carboxy)methoxy)methyl)-pyrrolidin-1-carboxylic acid tert-butylester (1.2 g, 4.5 mmol) in dichloromethane (20 ml) were added 1-hydroxy-7-azabenzotriazole (612 mg, 4.5 mmol) and 1-ethyl-3-(3-
20 dimethylaminopropyl)carbodiimide hydrochloride (950 mg, 4.95 mmol) and the mixture was stirred for 30 min. (2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (605 mg, 1.5 mmol) in dichloromethane (10 mL) was added followed by diisopropylethylamine (0.33 ml, 2.0 mmol) and the mixture was stirred for 2 hours at room temperature. The mixture
25 was washed with water (10 ml), aqueous sodium bicarbonate (10 ml), water (2 x 10 ml), brine (10 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (40 g) with ethyl acetate/heptane 4:1 to give 760 mg of (2S)-2-([N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-
30 naphthyl)ethyl]carbamoyl)methoxymethyl)pyrrolidine-1-carboxylic acid tert-butylester. The obtained product was taken up in 50% trifluoroacetic acid in methylene chloride (5 ml) and stirred for 10 min. Then saturated sodium

bicarbonate was added until pH 8 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The product was redissolved in water (30 ml) and acetic acid (2 ml) was added and the mixture was lyophilized to give 720 mg of the acetate salt of the title compound as an amorphous powder.

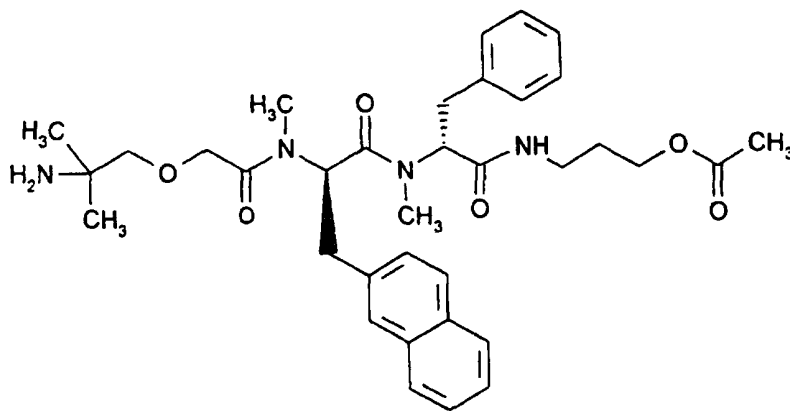
¹H-NMR (DMSO) (selected peaks): d 0.75 (m, 1H) 1.35 (m, 1H) 1.6 (m, 1H) 1.7 (m, 1H) 2.65 (d, 3H) 2.75 (d, 3H) 3.95 (d, 2H) 5.35 (dd, 1H) 5.55 (dd, 1H)

LC-MS : 544.8 (M+H)⁺

HPLC: R_t = 31.1 (Method A1)

Example 40

3-((2R)-2-(N-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate



To a solution of (2-t-butoxycarbonylamino-2-methylpropoxy) acetic acid (504 mg, 2.0 mmol) in dichloromethane (10 ml) were added 1-hydroxy-7-azabenzotriazole (278 mg, 2.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (429 mg, 2.3 mmol) and the mixture was stirred for 30 min. 3-((2R)-2-(N-((2R)-2-methylamino-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-propyl acetate (500 mg, 1.0 mmol) in dichloromethane (10 mL) was added followed by diisopropylethylamine (0.23 ml, 1.32 mmol) and the mixture was stirred overnight at room temperature. The mixture was washed with water (10 ml), aqueous sodium bicarbonate (10 ml), water (2 x 10 ml), brine (10 ml), dried over magnesium sulfate and concentrated *in vacuo*. The crude product was chromatographed on silica (60 g) with ethyl acetate/heptane 4:1 to give 623 mg of 3-((2R)-2-(N-((2R)-2-(N-((2-(tert-butoxycarbonylamino)-2-methylpropoxy) acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-propyl acetate as an oil. The obtained product was taken up in 50% trifluoroacetic acid in dichloromethane (3 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated *in vacuo*. The product was redissolved in water (30 ml) and the mixture was lyophilized to give 434 mg of the title compound as an amorphous powder.

¹H-NMR (CDCl₃) (selected peaks): d 1.1 (s, 3H) 1.2 (s, 3H) 2.0 (s, 3H) 2.15 (s, 3H) 5.7 (m, 2H) 5.25 (m, 1H)

LC-MS : 619.6 (M+H)⁺

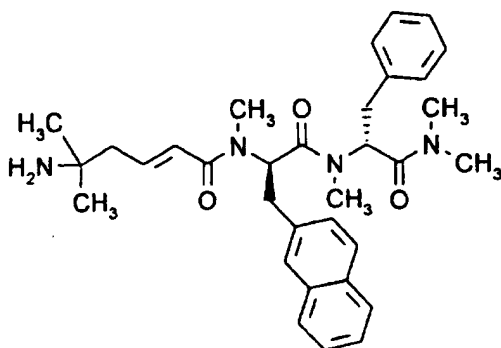
HPLC: R_t = 33.2 (Method A1)

25

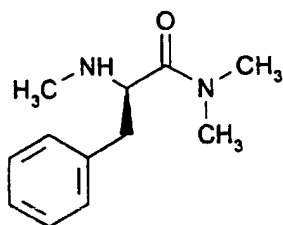
Example 41

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:

30



5 (2R)-N,N-Dimethyl-2-methylamino-3-phenylpropionamide



To a solution of (2R)-2-(tert-butoxycarbonylmethylamino)- 3-phenylpropionic acid (10.0 g, 36.0 mmol) in dichloromethane (200 ml) was added 1-hydroxy-7-azabenzotriazole (6.8 g, 50.0 mmol) and 1-ethyl-3-(3-

10 dimethylaminopropyl)carbodiimide hydrochloride (10.0 g, 55.0 mmol) and the mixture was stirred for 30 min. Then dimethylamine hydrochloride (4.1 g, 50.0 mmol) in dichloromethane (100 ml) and diisopropylethylamine (19.0 ml, 110 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (100 ml) aqueous sodium bicarbonate (100 ml),

15 water (2 x 100 ml), brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with dichloromethane/methanol 20:1 to give 6.3 g of (2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionic acid N,N-dimethylamide. The product was dissolved in 50% trifluoroacetic acid in dichloromethane (5 ml) and stirred for 10

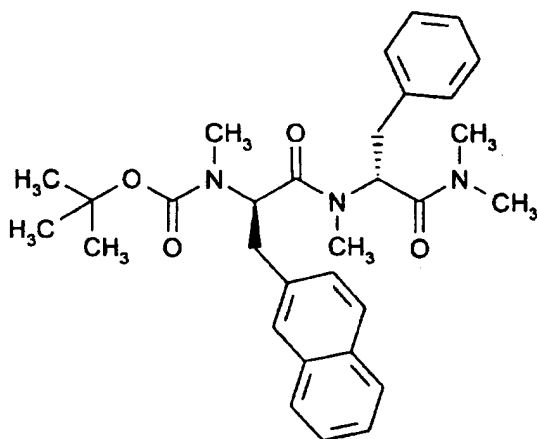
20 min. Then saturated sodium bicarbonate was added until pH 8 and the phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo to give 4.58 mg of (2R)-N,N-

dimethyl-2-methylamino-3-phenylpropionamide.

¹H-NMR (CDCl₃): d 2.3 (s, 3H) 2.7 (s, 3H) 2.9 (s, 3H) 2.8-3.4 (m, 2H) 4.45 (m, 1H) 7.1-7.3 (m, 5H)

5

N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester



To a solution of (2R)-(N-tert-butoxycarbonyl-N-methylamino)-3-

- 10 (2-naphthyl)propionic acid (8.78 g, 26.6 mmol) in dichloromethane (30 ml) were added 1-hydroxy-7-azabenzotriazole (3.62 g, 26.6 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.54 mg, 28.9 mmol) and the mixture was stirred for 30 min. Then (2R)-N,N-dimethyl-2-methylamino-3-phenylpropionamide (4.58 g, 22.2 mmol) in dichloromethane (15 ml) and
- 15 diisopropylethylamine (4.94 ml, 28.9 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (20 ml), aqueous sodium bicarbonate (20 ml), water (2 x 20 ml), brine (20 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with ethyl acetate/heptane 1:4 to give 6.64 g of
- 20 N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃) (selected peaks for rotamers): d 1.1 and 1.4 (two s, 9H) 2.2, 2.3, 2.7 and 2.8 (four s, 6H) 2.35 and 2.6 (two s, 3H) 2.9 and 3.0 (two s, 3H)

A solution of N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamamic acid tert-butylester (6.6 g, 12.8 mmol) in 50% trifluoroacetic acid/dichloromethane (15 ml) was stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 20 ml) and the combined organic phases were washed with brine (10 ml), dried over magnesium sulfate and concentrated in vacuo to give 4.2 g of (2R)-N-((1R)-1-dimethylcarbamoyl-2-phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

¹H-NMR (CDCl₃): δ 2.7 (s, 3H) 2.75 (s, 3H) 2.85 (s, 3H) 2.9-3.15 (m, 4H) 3.7 (t, 1H) 5.8 (t, 1H) 7.1-7.8 (arom, 12H)

To a solution of (2E)-5-(tert-butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.5 g, 2.1 mmol) in dichloromethane (5 ml) was added trifluoroacetic acid (5 ml) and stirred for 60 min and concentrated in vacuo. Then a 10% aqueous solution of sodium carbonate (30 ml) and dioxane (30 ml) were added followed by 9H-fluorenylmethyl-succinimidyl carbonate (0.67 g, 2.1 mmol) and stirred overnight. The mixture was washed with petrol ether (2 x 20 ml) and the aqueous layer was acidified with 4N sulphuric acid (pH~3) and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with 1N sulfuric acid, water (4 x 20 ml), brine (20 ml), dried (Magnesiumsulfate) and concentrated in vacuo. The obtained product was precipitated from dichloromethane/ether and filtered to give 280 mg of (2E)-5-(((9H-flouren-9-yl)methoxy)carbonylamino)-5-methyl-hex-2-enoic acid, which was used without further purification.

To a solution of (2E)-5-(((9H-flouren-9-yl)methoxy)-carbonylamino)-5-methylhex-2-enoic acid (280 mg, 0.77 mmol) in dichloromethane (5 ml) were added 1-hydroxy-7-azabenzotriazole (126 mg, 0.92 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (207 mg, 1.08 mmol) and the mixture was stirred for 30 min. Then 2R)-N-((1R)-1-dimethylcarbamoyl-2-

phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (386 mg, 0.92 mmol) in dichloromethane (5 ml) and diisopropylethylamine (0.17 ml, 1.00 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (20 ml), saturated aqueous sodium bicarbonate (20 ml), water (2 x 20 ml), brine (20 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with ethyl acetate/heptan 1:1 to give 401 mg of ((3E)-4-(N-((1R)-1-(N-((1R)-1-dimethylcarbamoyl-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid 9H-flouren-9-ylmethyl ester. The obtained product was dissolved in 20% piperidine in dimethylformamide (10 ml) and stirred for 30 min. The mixture was chromatographed on silica (20 g) with dichloromethane/methanol/ammonia 89:10:1 to give 228 mg of (2E)-5-amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide as an oil. The product was redissolved in water (30 ml) and acetic acid (2 ml) was added and the mixture was lyophilized to give 645 mg of the acetate salt of the title compound as an amorphous powder.

LC-MS : 543.0 (M+H)⁺

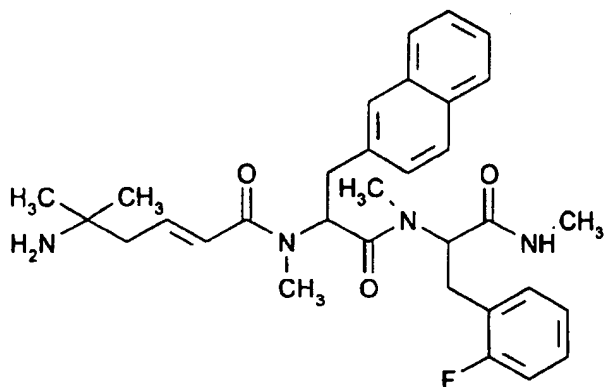
HPLC: R_t = 32.9 (Method A1)

¹H-NMR (DMSO) (selected peaks): d 1.0 (s, 6H) 1.8 (s, 6H) 2.4 (s, 3H) 2.7 (s, 3H) 2.8 (s, 3H)

Example 42

5-Amino-5-methyl-hex-2-enoic acid

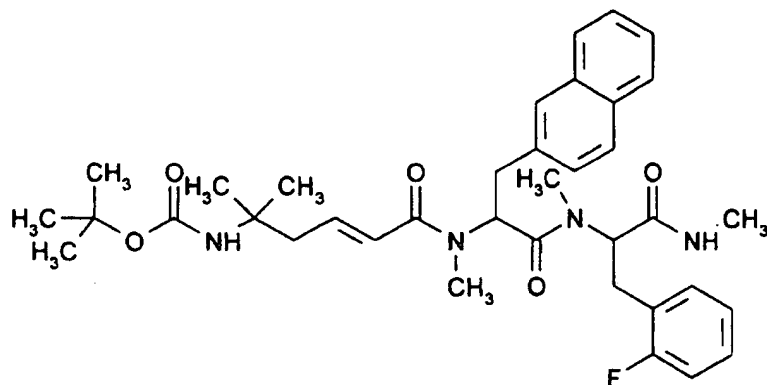
(1-[[2-(2-fluorophenyl)-1-methylcarbamoyl]methylcarbamoyl]-2-(2-naphthyl)ethyl)methylamide.



5

{4-[(1-[(2-(2-Fluorophenyl)-1-methylcarbamoyl)ethyl]methylcarbamoyl)-2-(2-naphthyl)ethyl]methylcarbamoyl]-1,1-dimethyl-but-3-enyl}carbamic acid tert-butyl ester.

10



15 (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.19 g; 0.783 mmol) was dissolved in methylene chloride (10 ml).

1-Hydroxy-7-azabenzotriazole (0.12 g; 0.861 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.17 g; 0.900 mmol) was

added and the reaction mixture was stirred 15 min at room temperature.

N-[2-(2-Fluorophenyl)-1-methylcarbamoylethyl]-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.33 g; 0.783 mmol) and diisopropyl ethylamine (0.15 ml; 0.861 mmol) was added and the reaction mixture was stirred 12 hours at room
5 temperature.

Methylene chloride (50 ml) was added and the reaction mixture was washed with water (50 ml), sodium hydrogen sulfate (10 %; 50 ml), sodium hydrogen carbonate (sat; 50 ml), water (50 ml) and dried (magnesium sulfate). The solvent was removed in vacuo to afford 0.366 g of

10 {4-[(1-[[2-(2-Fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl]-2-(2-naphthyl)ethyl)methylcarbamoyl]-1,1-dimethyl-but-3-enyl}carbamic acid tert-butyl ester.

{4-[(1-[[2-(2-Fluorophenyl)-1-methylcarbamoylethyl]methylcarbamoyl]-2-(2-naphthyl)ethyl)methylcarbamoyl]-1,1-dimethyl-but-3-enyl}carbamic acid tert-butyl ester (0.36

15 g; 0.557 mmol) was dissolved in methylene chloride (3 ml). Trifluoro acetic acid (3 ml) was added and the reaction mixture was stirred 5 min at room temperature.

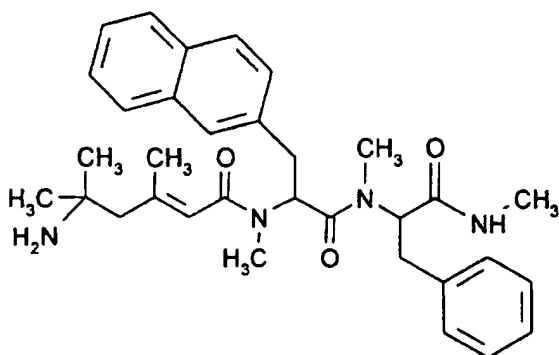
Methylene chloride (25 ml), sodium hydrogen carbonate/sodium carbonate (3 ml) and sodium hydrogen carbonate (s) was added until pH=8. The organic phase was dried (magnesium sulfate) and the solvent was removed in vacuo. The residue was

20 lyophilised to afford 0.237 g of the title compound.

Example 43

25 (2Z)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide.



5

(Z)(1,1,3-Trimethyl-4-(methyl-(1-(methyl-(1-methyl carbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl) ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester(0.009 g ; 0.014 mmol.) was dissolved in methylene chloride (0.12 mL) and trifluoro acetic acid (0.08 mL) was added. The reaction mixture was stirred 5
 10 min at room temperature. Water (0.100 mL) was added. The solvent was removed in vacuo to afford 0.007 g (2Z)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide ; trifluoro acetic acid salt.

15

ESMS : $M_w = 542.4$

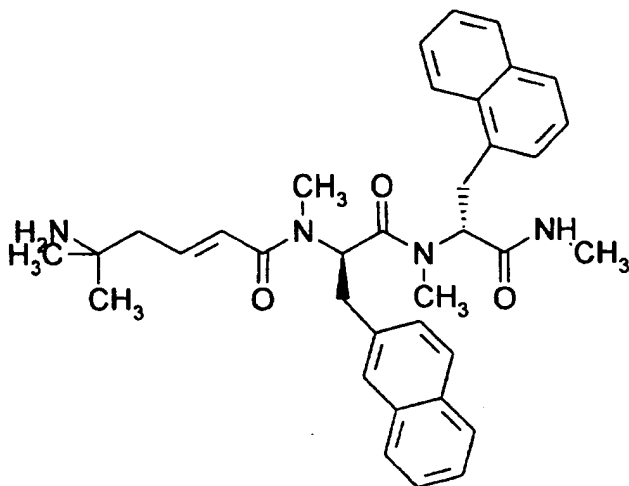
20

HPLC : $R_t = 34.82$

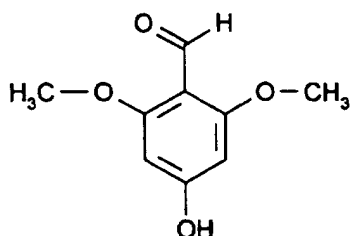
Example 44

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-

naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)amide:



5 4-Formyl-3,5-dimethoxyphenol:

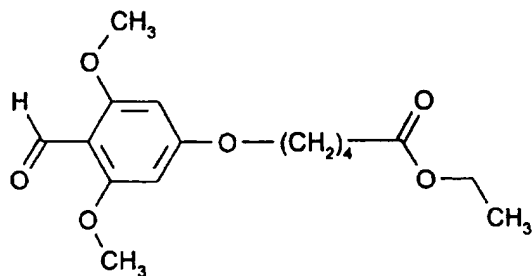


To a solution of 3,5-dimethoxyphenol (50 g, 320 mmol) in phosphorous
 10 oxychloride (60 mL, 650 mmol) at 0 °C was added dimethylformamide (37
 mL, 490 mmol) over a period of 30 min and the mixture was warmed to room
 temperature and stirred overnight. The mixture was added to icewater (600
 mL) and the mixture was washed with ether (3 x 200 mL). Then an 32 %
 aqueous solution of sodium hydroxide was added until pH was 5.5 and the
 15 compound precipitated. The precipitate was separated and washed with
 water (100 mL) and ether (100 mL) and dried in vacuo. The precipitate was
 recrystallized from ethanol (600 mL) to give 22.6 g of 4-formyl-3,5-
 dimethoxyphenol.

bp. 224-226 °C

¹H-NMR (DMSO): d 3.75 (s, 6H) 6.1 (s, 2H) 10.1 (s, 1H)

Ethyl 5-(4-formyl-3,5-dimethoxyphenoxy)valerate:



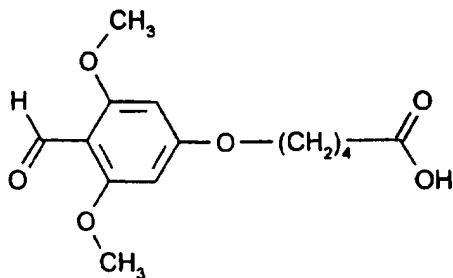
To a suspension of 4-formyl-3,5-dimethoxyphenol (22.6 g, 124 mmol) and potassium tert-butoxide (15.3 g, 136 mmol) in dimethylformamide (125 mL) was added ethyl 5-bromovalerate (28.5 g, 136 mmol) in dimethylformamide (125 mL) over a period of 20 min. The mixture was heated at 110 °C for 6 h and concentrated in vacuo. To the obtained product was added ethyl acetate (400 mL) and the mixture was filtered. The filtrate was washed with water (100 mL), 1 N sodium hydroxide (2 x 50 mL), and brine (3 x 100 mL), dried (magnesium sulfate), and concentrated in vacuo to 37 g of ethyl 5-(4-formyl-3,5-dimethoxyphenoxy)valerate.

10

15

¹H-NMR (CDCl₃): d 1.25 (t, 3H) 1.85 (m, 4H) 2.4 (m, 2H) 3.9 (s, 6H) 4.05 (t, 2H) 4.15 (q, 2H) 6.1 (s, 2H) 10.3 (1H)

5-(4-Formyl-3,5-dimethoxyphenoxy)valeric acid:



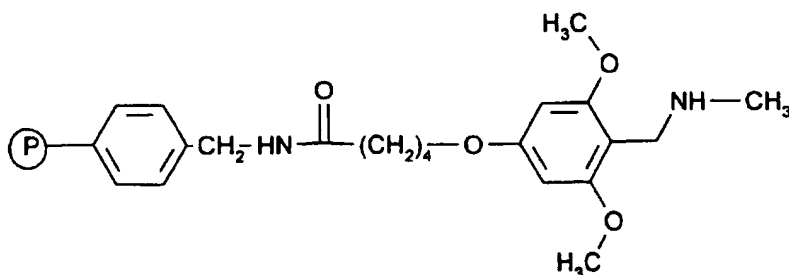
To a solution of ethyl 5-(4-formyl-3,5-dimethoxyphenoxy) valerate (37 g, 119 mmol) in methanol (200 mL) was added 4 N sodium hydroxide (200 mL) and

the mixture was stirred for 2 h. The methanol was removed in vacuo, water (100 mL) was added and the mixture was washed with ethyl acetate (100 mL) and dichloromethane (2 x 100 mL). The aqueous layer was acidified with 12 N hydrochloric acid until pH~3 and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (2 x 50 mL), dried (magnesium sulfate) and concentrated in vacuo. The obtained product was recrystallized from ethanol to give 26 g of 5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid.

bp. 134-136 °C

¹H-NMR (CDCl₃): δ 1.85 (m, 4H), 2.45 (m, 2H) 3.85 (s, 6H) 4.05 (m, 2H) 6.05 (s, 2H) 10.3 (s, 1H)

N-Methyl-PAL-Resin for Solid-Phase Synthesis (PAL defined as in F. Albericio et al., J. Org. Chem., **55** (1990) pp. 3730-3743) :



Aminomethylated polystyrene resin (10 g, 7.8 mmol, purchased from Bachem AG, # D-1005) and 1-hydroxybenzotriazole hydrate (1 g, 6.6 mmol) in dimethylformamide (100 mL) were shaken overnight. The resin was filtered and the resin was repeatedly swelled in dichloromethane and dimethylformamide until a homogeneous resin was obtained. The resin was washed with 5% diisopropylethylamine in dimethylformamide (2 x 100 mL) and dimethylformamide (100 mL), successively. A solution of 5-(4-formyl-3,5-dimethoxyphenoxy)valeric acid (6.6 g, 23 mmol), 1-hydroxybenzotriazole hydrate (3.5 g, 23 mmol) and diisopropylcarbodiimide (3.6 mL, 23 mmol) in dimethylformamide/dichloromethane 2:1 (50 mL) was added. After 5 h at

room temperature the resin was filtered and washed with dimethylformamide (3 x 100 mL), dichloromethane (3 x 50 mL) and dichloromethane/methanol 1:1 (3 x 100 mL) and dried with a stream of nitrogen.

To the resin in dimethylformamide (50 mL) were added 5% acetic acid in
5 dimethylformamide (50 mL) and 40 % methylamine in methanol (3.0 mL, 39 mmol) and the mixture was shaken for 20 min. Sodium triacetoxyborohydride (8.3 g, 39 mmol) was added and the mixture was shaken overnight. The mixture was filtered and the resin was washed with dimethylformamide (3 x 50 mL), dichloromethane (3 x 50 mL),
10 dichloromethane/methanol 1:1 (3 x 50 mL), ether (3 x 50 mL) and dried with a stream of nitrogen to give 10 g of N-Methyl-PAL-Resin (loading: 0.35-0.45 mmol/g based on N-analysis).

Calc: N 1.82 %

15 Found: N 1.47 %

The N-Methyl-PAL-Resin (450 mg) was washed with 5 % diisopropylethylamine in dichloromethane (2 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (3 x 2 mL) and then swelled in
20 dimethylformamide (7 mL). Then (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid (163 mg, 0.36 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.36 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36
25 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (123 mL, 0.72 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5
30 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then (2R)-2-(N-((9H-fluoren-9-

yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (163 mg, 0.36 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.36 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (123 ml, 0.72 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then (2E)-5-(N-tert-butoxycarbonylamino)-5-methylhex-2-enoic acid (88 mg, 0.36 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (137 mg, 0.36 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (49 mg, 0.36 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (123 mL, 0.72 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). The resin was cooled to 0 °C and 50 % trifluoroacetic acid in dichloromethane (4 mL) was added and the mixture was shaken for 10 min at 0 °C. The resin was filtered and washed with 50 % trifluoroacetic acid in dichloromethane (2 x 0.5 mL) and the combined filtrates were concentrated under a stream of nitrogen. The obtained product was dissolved in acetonitrile/water 1:20 (10 mL) and applied to a C-18 Sep-Pak Classic® cartridge (0.25 g, purchased from Waters™), which had been prewashed with acetonitrile (10 mL) and water (10 mL). Then water/trifluoroacetic acid 99.9:0.1 (5 mL), followed by water/acetonitrile/trifluoroacetic acid 89.9:10:0.1 (4 mL) was run through the Sep-Pak® and the filtrate was discarded. Then the Sep-Pak was washed with water/acetonitrile/trifluoroacetic acid 64.9:35:0.1 (4 mL) and the filtrate was

diluted with water (11 mL) and lyophilized to 52 mg of the title product.

HPLC: (A1) $R_t = 35.03$ min

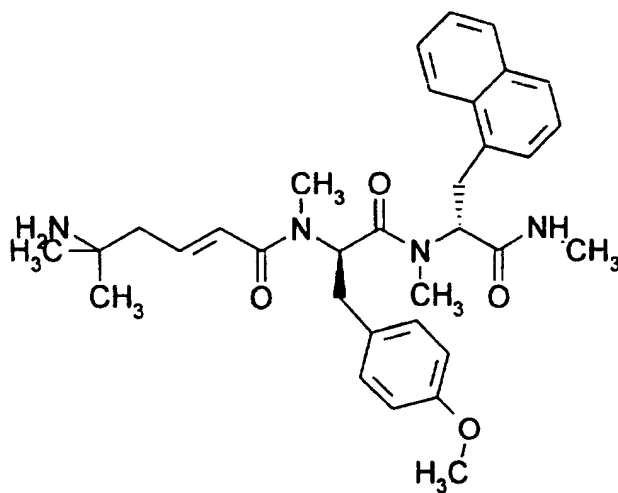
(B1) $R_t = 36.93$ min

5

LC-MS: 579.0 (m+1)⁺

Example 45

- 10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-[N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl]-2-(4-methoxyphenyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

20

Yield: 44 mg

HPLC:(A1) R_t = 30.22 min

(B1) R_t = 32.10 min

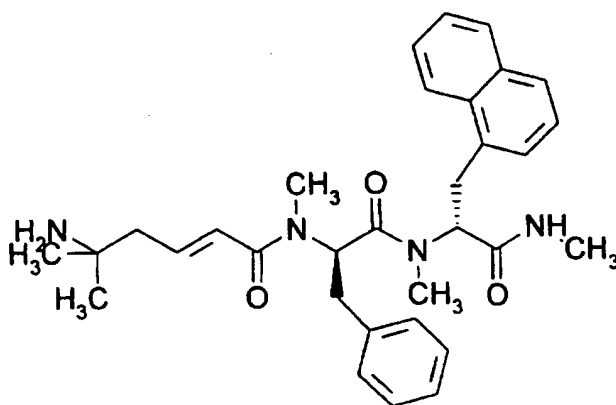
LC-MS: 559.2 (m+1)⁺

5

Example 46

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-[(1R)-2-(1-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl)-2-

10 phenylethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-20 (2-naphthyl)propionic acid.

Yield: 38 mg

HPLC:(A1) R_t = 30.68 min

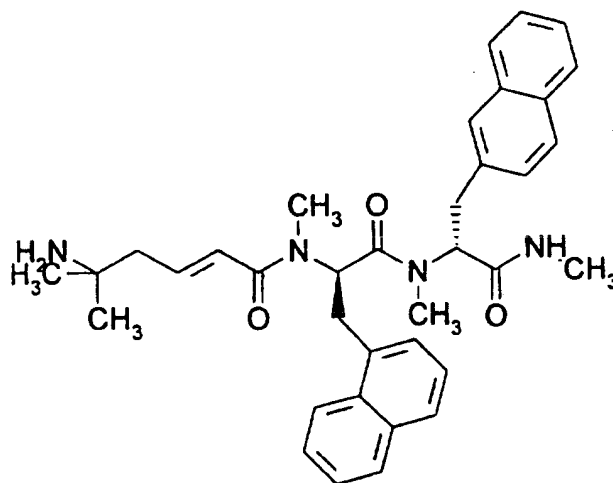
(B1) $R_t = 32.33$ min

LC-MS: 529.0 (m+1)⁺

5 Example 47

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:

10



The title compound was prepared analogously to example 44 with (2R)-2-(N-
 15 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic
 acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-
 methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-
 yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid instead of
 (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-
 20 naphthyl)propionic acid.

Yield: 70 mg

HPLC: (A1) $R_t = 34.52$ min

(B1) $R_t = 36.38$ min

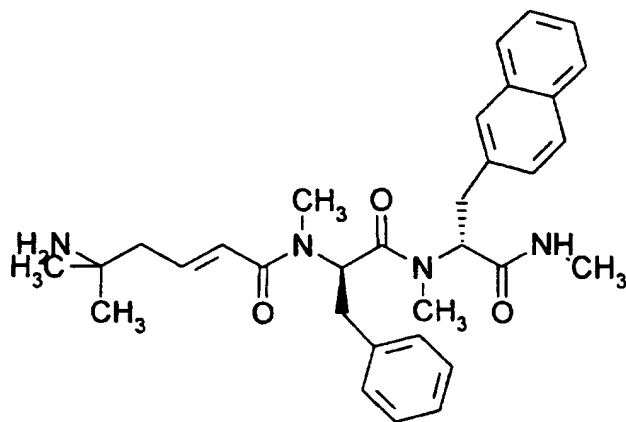
LC-MS: 579.0 (m+1)⁺

5

Example 48

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-[(1R)-2-(2-naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl)-2-

10 phenylethyl)amide:



15 The title compound was prepared analogously to example 44 (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid instead of
20 (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 49 mg

HPLC: (A1) $R_t = 30.52$ min

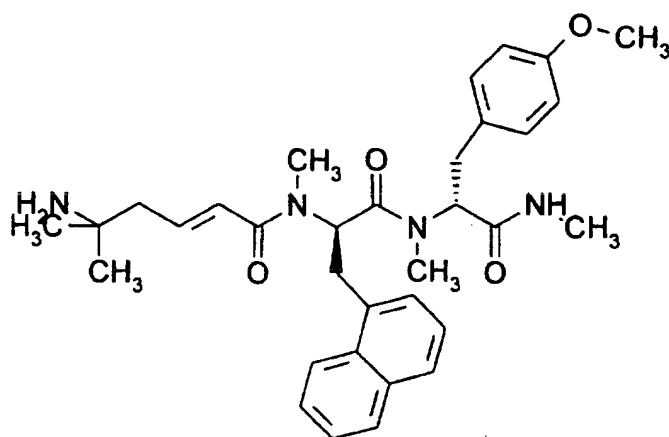
(B1) $R_t = 32.03$ min

LC-MS: 529.0 (m+1)⁺

5

Example 49

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 51 mg

HPLC: (A1) $R_t = 30.20$ min

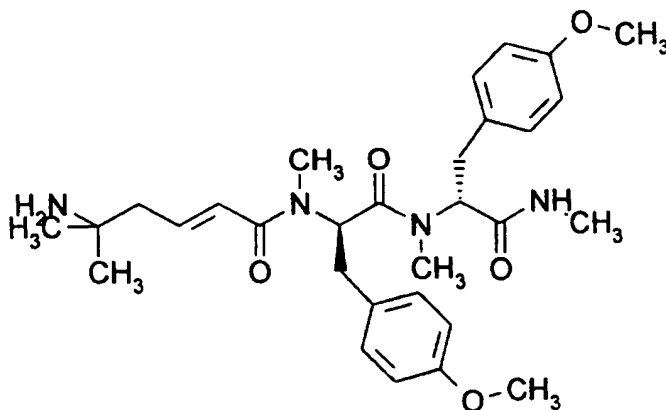
(B1) $R_t = 31.70$ min

5

LC-MS: 559.2 (m+1)⁺

Example 50

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 26 mg

HPLC: (A1) $R_t = 25.75$ min

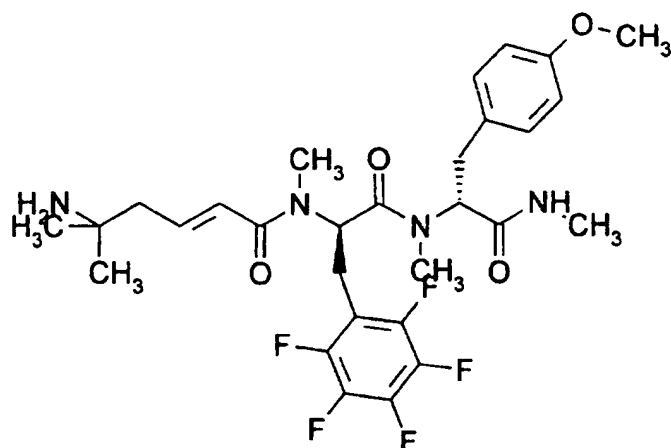
(B1) $R_t = 26.98$ min

5

LC-MS: 539.2 ($m+1$)⁺

Example 51

- 10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl)-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide:



15

- The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.
- 20

Yield: 42 mg

HPLC: (A1) $R_t = 31.05$ min

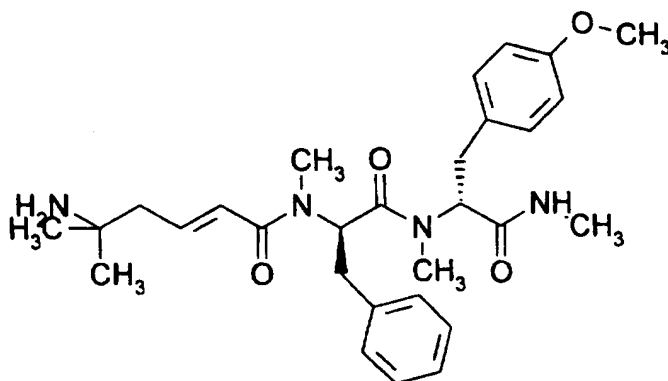
5 (B1) $R_t = 32.00$ min

LC-MS: 599.0 (m+1)⁺

Example 52

10

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid
20 instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid
instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

25

Yield: 31 mg

HPLC: (A1) $R_t = 25.68$ min

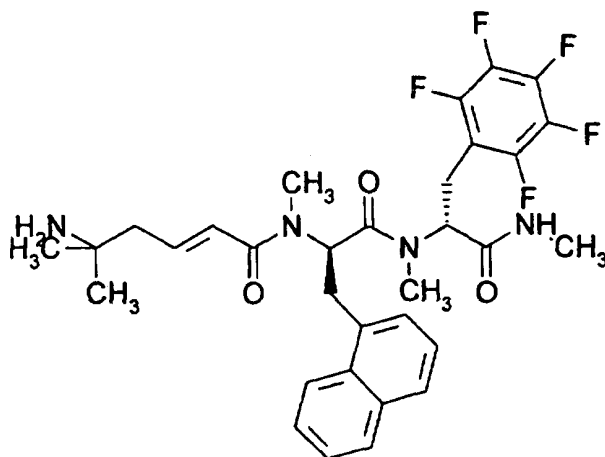
(B1) $R_t = 27.00$ min

5

LC-MS: 509.2 (m+1)⁺

Example 53

- 10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide:



15

The title compound was prepared analogously to example 44 with (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-

20

yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 38 mg

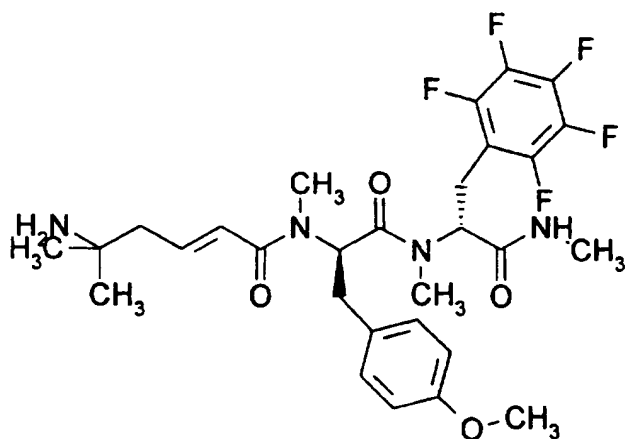
5 HPLC: (A1) $R_t = 34.88$ min
(B1) $R_t = 36.78$ min

LC-MS: 619.0 (m+1)⁺

10 Example 54

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:

15



The title compound was prepared analogously to example 44 with (2R)-2-(N-
20 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-

yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 25 mg

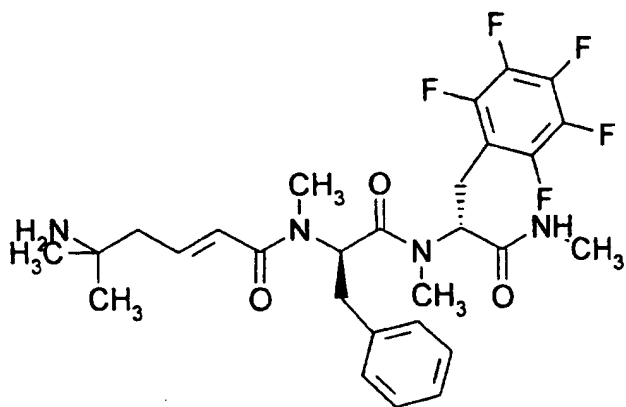
5 HPLC: (A1) $R_t = 30.72$ min
(B1) $R_t = 32.32$ min

LC-MS: 599.0 (m+1)¹

10 **Example 55**

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide:

15



The title compound was prepared analogously to example 44 with (2R)-2-(N-
20 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid
instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-
(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-
yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-
pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-
25 yl)methoxycarbonyl)-N-methylamino)-3-(1-naphthyl)propionic acid.

Yield: 30 mg

HPLC: (A1) $R_t = 30.88$ min

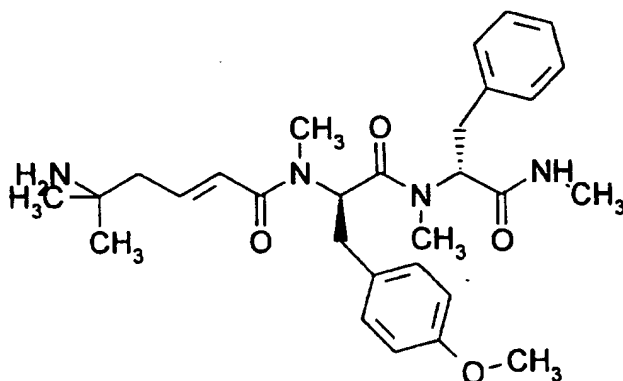
5 (B1) $R_t = 32.55$ min

LC-MS: 569.0 (m+1)⁺

Example 56

10

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide:



The title compound was prepared analogously to example 44 with (2R)-2-(N-
20 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(4-methoxyphenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-
25 methylamino)-3-(1-naphthyl)propionic acid.

Yield: 25 mg

HPLC: (A1) R_t = 25.95 min

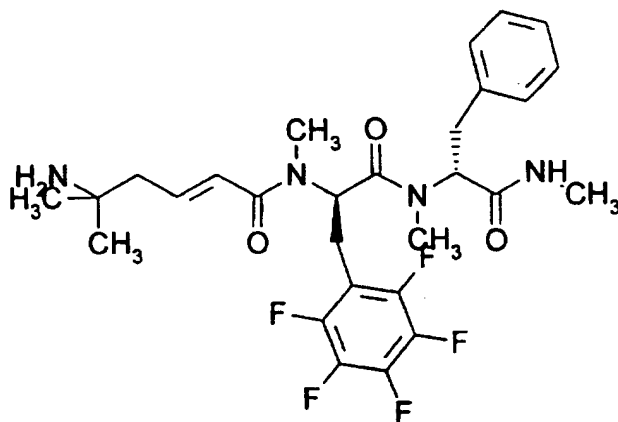
5 (B1) R_t = 27.23 min

LC-MS: 509.4 (m+1)⁺

Example 57

10

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide:



The title compound was prepared analogously to example 44 with (2R)-2-(N-
20 ((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2,3,4,5,6-
pentafluorophenyl)propionic acid instead of (2R)-2-(N-((9H-fluoren-9-
yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid and (2R)-
2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-phenylpropionic
acid instead of (2R)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-

methylamino)-3-(1-naphthyl)propionic acid.

Yield: 35 mg

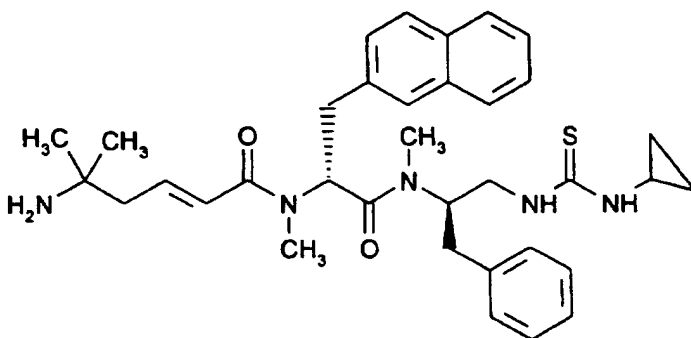
5 HPLC: (A1) $R_t = 31.20$ min
(B1) $R_t = 32.47$ min

LC-MS: 569.0 (m+1)¹

10 Example 58

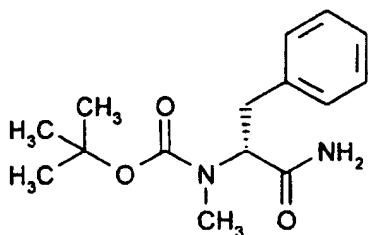
(2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-N-
((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-3-(2-
naphthyl)propionamide

15



20

N-((1R)-1-Carbamoyl-2-phenylethyl)-N-methylcarbamic acid tert.-butylester.



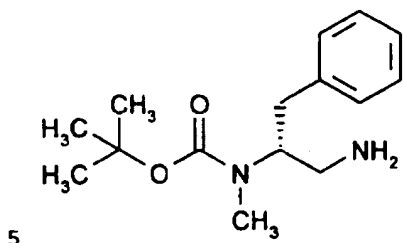
5

A solution of (2R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-phenylpropionic acid (4.00 g, 14.32 mmol) in N,N-dimethylformamide (10 ml) was cooled to 0 °C. Ammonium hydrogen carbonate (5.66 g, 71.60 mmol) was added as a solid. 1-Hydroxybenzotriazole hydrate (1.94 g, 14.32 mmol) and successively N-(3-
10 dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.75 g, 14.32 mmol) were added. The suspension was stirred for 16 h, while warming up to room temperature. The reaction mixture was diluted with ethyl acetate (150 ml) and extracted with saturated sodium chloride solution/water (200 ml/300 ml). The aqueous phase was extracted with ethyl acetate (3 x 100 ml). The combined
15 organic layers were washed with saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash-chromatography on silica (70 g), using ethyl acetate/heptane as eluent, to give 2.80 g of N-((1R)-1-carbamoyl-2-phenylethyl)-N-methylcarbamic acid tert.-butylester.

20

¹H-NMR (CDCl₃): δ 1.29 and 1.40 (both s, together 9H); 2.74 (s, 3H); 2.95 (m, 1H); 3.37 (m, 1H); 4.75 and 4.96 (both m, together 1H); 5.55, 5.73, 5.95, and 6.17 (all br,
25 together 2 H); 7.05 - 7.40 (m, 5H).

N-((1R)-1-Aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

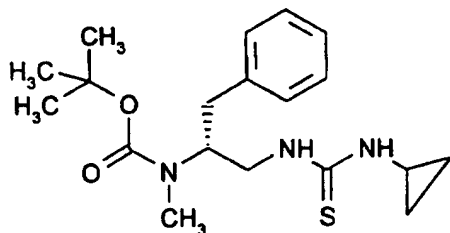


N-((1R)-1-Carbamoyl-2-phenylethyl)-N-methylcarbamic acid tert.-butylester (2.73 g,
10 9.81 mmol) was dissolved in tetrahydrofuran (10 ml). The solution was cooled to 5
°C. A suspension of sodium borohydride (816 mg, 21.58 mmol) in tetrahydrofuran
(10 ml) was added. A solution of iodine (1.24 g, 4.91 mmol) was added dropwise.
After the addition was completed, the solution was heated to reflux for 16 h. It was
cooled to 5 °C. A 10% solution of ammonium chloride in water (60 ml) was added
15 dropwise. The solution was warmed to 50 °C for 1 h. It was cooled to room
temperature. 1 N sodium hydroxide solution was added until pH 14. It was
extracted with tert-butyl methyl ether (4 x 100 ml). The combined organic layers
were dried over magnesium sulfate. The solvent was removed in vacuo. The crude
product was purified by flash chromatography on silica (150 g) using
20 dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent to give 453
mg of N-((1R)-1-aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃): d 1.29 and 1.36 (both s, together 9 H); 2.60 - 2.90 (m, 7 H); 4.20
25 and 4.38 (both br, together 1 H); 7.10 - 7.35 (m, 5 H).

N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamic acid tert-butylester.

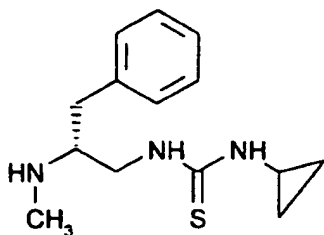
5



- 10 At 0 °C, cyclopropylisothiocyanate (0.32 ml) was added to a solution of N-((1R)-1-aminomethyl-2-phenylethyl)-N-methylcarbamic acid tert-butylester (410 mg, 1.6 mmol) in dichloromethane (4 ml). The reaction mixture was first stirred at 0 °C for 10 min, and successively for 2.5 h at room temperature. The solvent were removed in vacuo. The crude product was purified by flash chromatography on silica (50 g)
- 15 using ethyl acetate/heptane as eluent to give 492 mg of N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamic acid tert-butylester.

- 20 ¹H-NMR (CDCl₃): δ 0.62 (br, 2 H); 1.26 and 1.36 (both s, together 9 H); 2.37 (br, 1 H); 2.60 - 3.00 (m, 5 H); 3.60 (m, 1 H); 3.98 (m, 1 H); 4.60 (m, 1 H); 6.30 and 6.85 (both m, together 2 H); 7.10 - 7.35 (m, 5 H).

N-Cyclopropyl-N'-((2R)-2-methylamino)-3-phenylpropylthiourea.

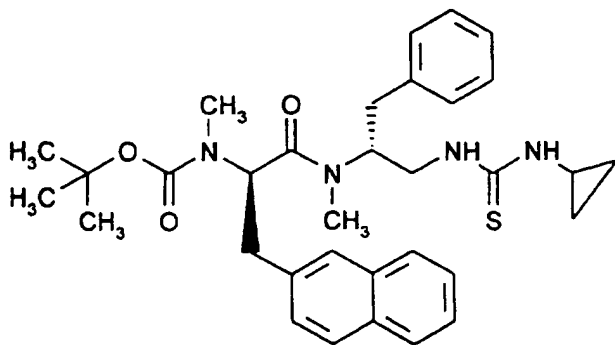


N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamic acid tert-butylester (404 mg, 1.1 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (2 ml) was added. The reaction mixture was stirred for 7 min. The solvents were removed in vacuo. The residue was dissolved in dichloromethane and the solvent was removed in vacuo. This latter procedure was repeated two times. The crude product was purified by flash chromatography on silica (9 g), using dichloromethane/methanol/25% aqueous ammonia (100:10:1) as eluent, to give 255 mg of N-cyclopropyl-N'-((2R)-2-methylamino)-3-phenylpropylthiourea.

¹H-NMR (CDCl₃): d 0.64 (br, 2 H); 0.85 (m, 2 H); 2.38 (s, 3 H); 2.45 (m, 1 H); 2.77 (ABX, 2 H); 2.99 (m, 1 H); 3.58 (m, 1 H); 3.74 (m, 1 H); 6.25 (m, 1 H); 7.15 (m, 1 H); 7.15 - 7.35 (m, 5 H).

N-((1R)-1-(N-((1R)-1-((3-Cyclopropylthioureido)methyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

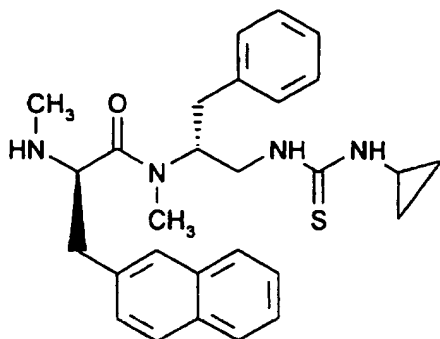
20



(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (290 mg, 0.88 mmol) was dissolved in dichloromethane (2 ml) and N,N-dimethylformamide (2 ml). 1-Hydroxy-7-azabenzotriazole (120 mg, 0.88 mmol) was added as a solid. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (202 mg, 1.06 mmol) was added. The solution was stirred for 20 min. N-Cyclopropyl-N'-((2R)-2-methylamino)-3-phenylpropylthiourea (231 mg, 0.88 mmol) was dissolved in dichloromethane (2 ml) and added. The reaction mixture was stirred for 16 h. It was diluted with ethyl acetate (100 ml) and extracted with 1 N hydrochloric acid (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (45 g) using ethyl acetate/heptane 1:1 as eluent to give 350 mg of N-((1R)-1-(N-((1R)-1-((3-Cyclopropylthioureido)methyl)-2-phenyl-ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃): δ 0.06, 0.19, 0.30, 0.40, 0.55 (all m, together 4 H); 1.25 and 1.33 (both s, together 9 H); 1.41 and 1.60 (both m, together 1 H); 2.12 and 1.27 (both s, together 3 H); 2.70 - 3.00 (m, 6 H); 3.25 (m, 1 H); 3.55 (m, 1 H); 4.00 and 4.15 (both m, together 1 H); 5.02 and 5.37 (both t, together 1 H); 5.12 and 5.25 (both m, together 1 H); 5.90 and 5.99 (both br, together 1 H); 6.60 (m, 1 H); 7.10 - 7.85 (m, 12 H).

(2R)-N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.



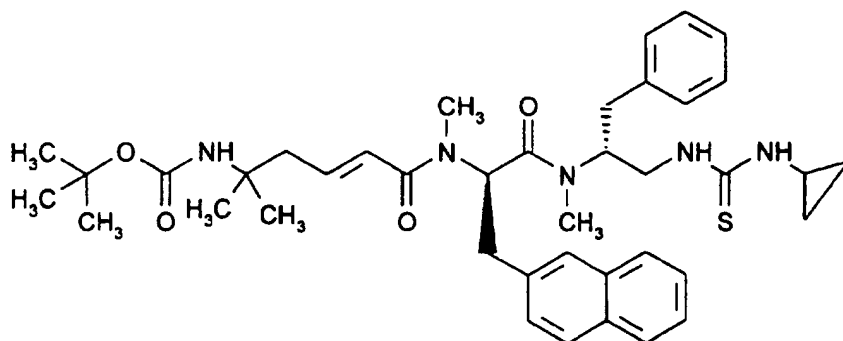
N-((1R)-1-(N-((1R)-1-((3-Cyclopropylthioureido)methyl)-2-phenylethyl)-

- 5 N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamic acid tert-butylester (579 mg, 1.01 mmol) was dissolved in dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (2 ml) was added. The solution was stirred for 5 min. The solvents were removed in vacuo without warming. The residue was dissolved in dichloromethane (100 ml) and the solvent was removed in vacuo. This latter
- 10 procedure was repeated two times. The crude product was purified by flash chromatography on silica (45 g) using dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent to give 201 mg of (2R)-N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

- 15 ¹H-NMR (CDCl₃): d 0.63 (m, 2H); 0.85 (m, 2 H); 1.90 (s, 3 H); 2.38 (br, 1 H); 2.65 (s, 3 H); 2.70 - 3.05 (m, 5 H); 3.60 (m, 1 H); 4.05 (m, 1 H); 5.23 (m, 1 H), 6.30 (m, 1 H); 6.90 - 7.85 (m, 13 H).

(3E)-4-(N-((1R)-1-(N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-

- 20 N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butylester



- (2E)-5-tert-Butoxycarbonylamino-5-methylhex-2-enoic acid (182 mg, 0.75 mmol) was dissolved in N,N-dimethylformamide (2 ml) and dichloromethane (2 ml). 1-Hydroxy-7-azabenzotriazole (102 mg, 0.75 mmol) was added. The solution was cooled to 0 °C. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (144 mg, 0.75 mmol) was added. The solution was stirred for 15 min at 0 °C. (2R)-N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (178 mg, 0.37 mmol) was dissolved in dichloromethane and added to the reaction mixture. Ethyldiisopropylamine (0.13 ml, 0.75 mmol) was added. The solution was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (200 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (100 ml). The aqueous solution was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (150 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (45 g) to give 89 mg of (3E)-4-(N-((1R)-1-(N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butylester.

¹H-NMR (CDCl₃, selcted values): d -0.08, 0.11, 0.20, 0.30, and 0.60 (all m, together 4 H); 3.34 (dd, 1 H); 4.00 (m, 1 H); 5.52 and 5.87 (dd, 1 H); 6.00 and 6.05 (both d, together 1 H); 6.65 and 6.80 (both m, together 1 H).

(3E)-4-(N-((1R)-1-(N-((1R)-1-Benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylcarbamoyl)-1,1-dimethylbut-3-enylcarbamic acid tert-butylester (63 mg, 0.09 mmol) was dissolved in
5 dichloromethane (2 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (2 ml) was added. The solution was stirred for 15 min at 0 °C. The solvent was removed in vacuo at 20 °C. The residue was dissolved in dichloromethane (50 ml), and the solvent was removed in vacuo. This latter procedure was repeated two times. The residue was dissolved in ethyl acetate (2 ml). Heptane (5 ml) was added. The
10 precipitation was filtered off and was characterized to be 50 mg of the title compound as trifluoroacetic acid salt.

¹H-NMR (DMSO-d₆, selected values): δ 0.25 - 0.75 (m, 4 H); 3.15 (dd, 1 H); 6.41
15 (m, 1 H).

HPLC:

The RP-HPLC analysis was performed using UV detection at 254nm and a Lichrosorp RP-18 5mM column, which was eluted at 1ml/minute. Two solvent
20 systems were used:
Solvent system I: 0.1% Trifluoro acetic acid in acetonitrile. Solvent system II: 0.1% Trifluoroacetic acid in water.
The column was equilibrated with a mixture composed of 20% of solvent system I and 80% of solvent system II. After injection of the sample a gradient of 20% to
25 80% of solvent system I in solvent system II was run over 30 minutes. The gradient was then extended to 100% of solvent system I over 5 minutes followed by isocratic elution with 100% of this system for 6 minutes.

R_t 20.42 min.

30

MS: found 599.6 [M+H]⁺, calc: 599.3.

m.p.: 138 - 145 °C.

$C_{35}H_{45}N_5O_2S \cdot CF_3COOH \cdot 2 H_2O$

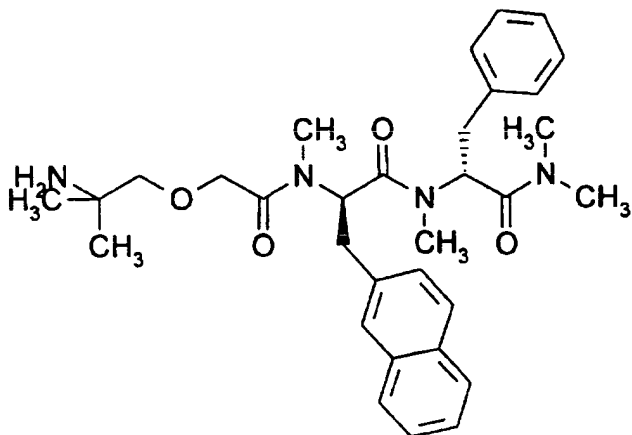
5 calc.: C 59.26 H 6.72 N 9.34

found: C 59.23 H 6.64 N 8.83.

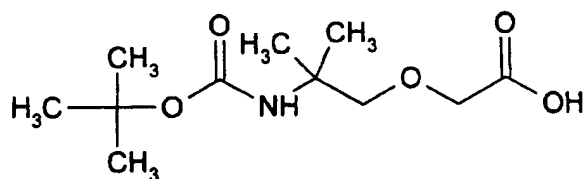
Example 59

10

(2R)-2-(N-[(2-Amino-2-methylpropoxy)acetyl]-N-methylamino)-N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide:



15 (2-tert-Butoxycarbonylamino-2-methylpropoxy)acetic acid:



A solution of 2-tert-butoxycarbonylamino-2-methylpropanol (5.0 g, 26 mmol) and rhodium(II)acetate (90 mg) in 1,2-dichloroethane (500 ml) was heated to 80 °C. Then ethyl diazoacetate (4.0 g, 35 mmol) was added over a period of 1 h, and the mixture was stirred at reflux for 3 h. Another portion of rhodium(II)acetate (90 mg) was added and the mixture was refluxed for

another 5 h. The mixture was cooled overnight and saturated sodium bicarbonate (500 ml) was added, the phases were separated and the organic layer was washed with saturated sodium bicarbonate (2 x 200 ml), dried (magnesium sulfate) and concentrated in vacuo. The obtained product
5 was dissolved in 1 M lithium hydroxide in methanol/water 3:1 (200 ml) and stirred overnight. The solvent was removed in vacuo, water was added (pH>9) and the mixture was washed with ether (200 ml). Then 1 M hydrochloric acid was added until pH<4 and the mixture was extracted with ethyl acetate (200 ml), dried (magnesium sulfate) and concentrated in vacuo
10 to give 2.5 g of (2-tert-butoxycarbonylamino-2-methylpropoxy)acetic acid.

¹H-NMR (CDCl₃): δ 1.3 (s, 6H) 1.45 (s, 9H) 3.5 (s, 2H) 4.15 (s, 2H) 9.9 (b, 1H).

15 To a solution of (2-tert-butoxycarbonylamino-2-methylpropoxy)acetic acid (480 mg, 1.9 mmol) in dichloromethane (10 ml) were added 1-hydroxy-7-azabenzotriazole (264 mg, 1.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (409 mg, 2.1 mmol) and the mixture was stirred for 30 min. Then (2R)-N-((1R)-1-dimethylcarbamoyl-
20 2-phenylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (434 mg, 0.97 mmol) in dichloromethane (5 ml) and diisopropylethylamine (0.22 ml, 1.3 mmol) were added and the mixture was stirred overnight at room temperature. The mixture was washed with water (20 ml), saturated aqueous sodium bicarbonate (20 ml), water (2 x 20 ml), brine (20 ml), dried
25 over magnesium sulfate and concentrated in vacuo. The crude product was chromatographed on silica (400 g) with ethyl acetate/pentane 7:3 to give 432 mg of (2-[[N-((1R)-1-[N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl]-2-(2-naphthyl)ethyl)-N-methylcarbamoyl]methoxy]-1,1-dimethylethyl)carbamic acid tert-butylester. The obtained product was
30 dissolved in 50% trifluoroacetic acid in dichloromethane (3 ml) and stirred for 10 min. Then saturated sodium bicarbonate was added until pH 8 and the

phases were separated. The aqueous phase was extracted with dichloromethane (2 x 10 ml) and the combined organic phases were washed with brine (5 ml), dried (magnesium sulfate) and concentrated in vacuo. The product was redissolved in water (30 ml) and the mixture was lyophilized to
5 give 300 mg of the title compound.

¹H-NMR (CDCl₃) (selected peaks): d 1.2 (d, 6H) 2.2 (s, 6H) 2.7 (s, 3H) 2.8 (s, 3H) 4.0 (q, 2H) 5.7 (m, 1H) 5.8 (m, 1H) 7.1-7.8 (m, 12H).

10 HPLC (A1): R_t = 32.8

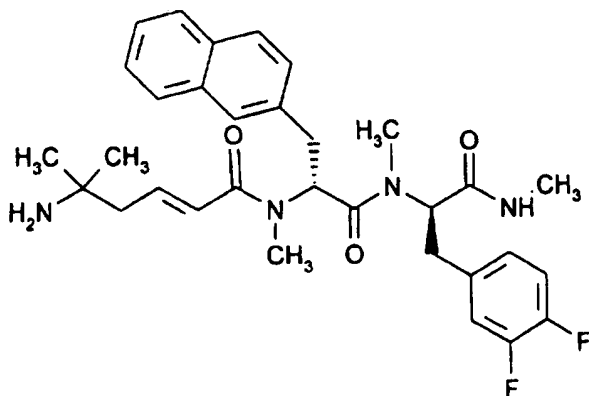
(B1): R_t = 34.6

LC-MS: 547.0 (M+H)⁺

15

Example 60

5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
2-(3,4-difluorophenyl)-1-methylcarbamoyl)ethyl)methylcar-
20 bamoyl)-2-(2-naphthyl)ethyl)methylamide



This compound was prepared analogously to example 1. 2-(3,4-difluorophenyl)-alanine was substituted for phenylalanine.

5 ¹H-NMR (CDCl₃): (selected peaks for major rotamer) d 1.22 (s, 6H); 2.10 (d, 3H); 2.71 (s, 3H); 2.85 (s, 3H); 5.22 (dd, 1H); 5.86 (dd, 1H); 6.17 (d, 1H).

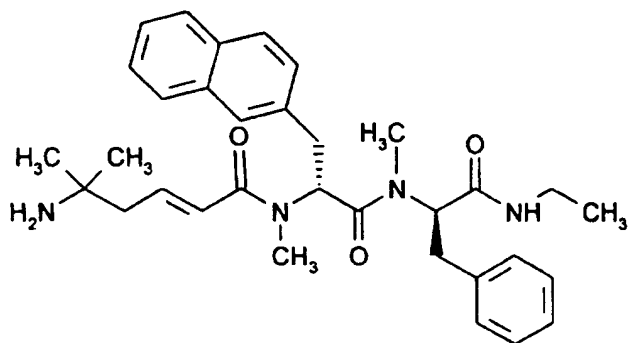
HPLC : r_t = 33.18 min. (A1)

PDMS : m/z 566.0 (M+H)⁺

10

Example 61

5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-
15 2-phenyl-1-ethylcarbamoylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide



20 This compound was prepared analogously to example 1.

¹H-NMR (CDCl₃): (selected peaks for major rotamer) d 0.61 (t, 3H); 1.05 (s, 6H); 1.98 (s, 3H); 2.24 (s, 3H); 2.97 (d, 3H); 5.57 (dd, 1H); 5.85 (dd, 1H); 6.07 (d, 1H).

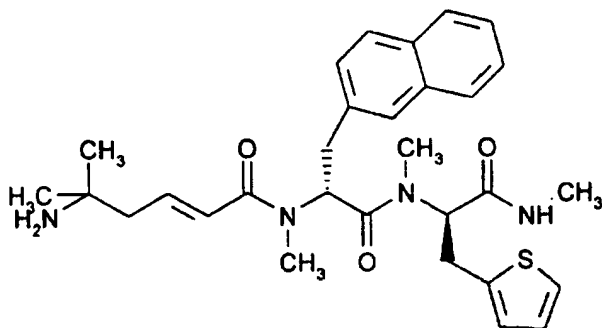
25 HPLC : r_t = 33.0 min (A1)

PDMS : m/z 544.0 (M+H)⁺

Example 62

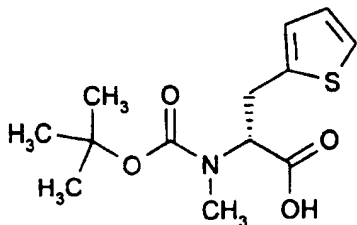
5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide



10

15 (2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(thiophen-2-yl)propionic acid



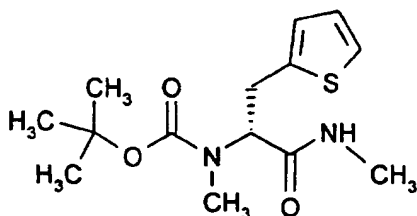
20 (2R)-2-(tert-Butoxycarbonylamino)-3-(thiophen-2-yl)propionic acid (5.00 g; 18.4 mmol) was dissolved in tetrahydrofuran (60 ml). Methyl iodide (9.2 ml; 147 mmol) was added and the solution was cooled to 0°C. Sodium hydride (60 % in oil; 1.90 g;

55.3 mmol) was added in portions and the reaction mixture was stirred at room temperature for two days. Ethyl acetate (50 ml) and water (20 ml) were added dropwise. The solvent was removed in vacuo and the residue was dissolved in ether (30 ml) and water (30 ml). The phases were separated and the organic phase
5 was washed with saturated aqueous sodium hydrogencarbonate (30ml). The aqueous phase were mixed. Citric acid (5% (aq)) was added to pH 3 and the aqueous phase was extracted with ethyl acetate (4 x 30 ml). The combined organic phases were washed with water (2 x 30 ml), aqueous sodium thiosulfate (5%; 30 ml), water (30 ml) and dried over magnesium sulfate. The solvent was removed in
10 vacuo. The residue was dissolved in ether (10 ml) and dicyclohexylamine (8.5 ml) was added and the mixture was left in a refrigerator overnight. The precipitate was filtered and washed with ether (2 x 15 ml) and then redissolved in methylene chloride and washed with a mixture of water (15 ml) and sodium hydrogensulfate (15 ml; 10 %(aq)). The aqueous phase was washed with methylene chloride (3 x 15
15 ml). The combined organic phases were dried over magnesium sulfate and the solvent was removed in vacuo to give 5.10 g of (2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(thiophen-2-yl)propionic acid.

20

¹H-NMR: (CDCl₃) (major rotamer) δ 1.38 (s, 9H); 2.85 (s, 3H); 3.14 (dd, 1H); 3.56 (dd, 1H); 4.62 (dd, 1H); 6.80-7.11 (3 arom. H).

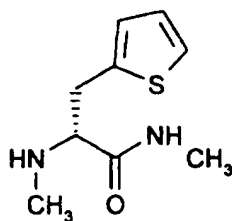
25 N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamic acid tert-butylester



(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(thiophen-2-yl)propionic acid (2.00 g; 7.01 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxybenzotriazole (0.95 g; 7.01 mmol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (1.48 g; 7.71 mmol) were added. The solution was stirred for 15 min. at room temperature. Methylamine (40 % in methanol; 0.38 ml; 7.71 mmol) and diisopropylamine (1.2 ml; 7.01 mmol) were added and the reaction mixture was stirred at room temperature for two days. Water (10 ml) and methylene chloride (10 ml) were added to the solution. The phases were separated and the organic phase was washed with aqueous sodium hydrogensulfate (10%; 15 ml), saturated aqueous sodium hydrogencarbonate (15 ml), dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was chromatographed on silica (4 x 40 cm) with ethyl acetate/methylene chloride (1:1) as eluent to give 1.18 g of N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamic acid tert-butylester.

¹H-NMR : (CDCl₃) (major rotamer) δ 1.42 (s, 9H); 2.80 (s, 6 H); 3.20 (m, 1H); 3.49 (dd, 1H); 4.92 (dd, 1H); 6.81- 7.18 (arom.; 3H).

(2R)-N-Methyl-2-methylamino-3-(thiophen-2-yl)propionamide



N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamic acid tert-butylester (1.17 g; 3.92 mmol) was dissolved in methylene chloride (4 ml). The reaction was cooled to 0°C and trifluoroacetic acid was added. The mixture was stirred at room temperature for 1.5 hour. Water (30 ml) and solid sodium

hydrogencarbonate were added to pH 8. The phases were separated. The aqueous phase was extracted with methylene chloride (4 x 20 ml). The combined organic phases were dried over magnesium sulfate and the solvent was removed over vacuo to afford 0.70 g of

5 (2R)-N-methyl-2-methylamino-3-(thiophen-2-yl)propionamide.

¹H-NMR : (CDCl₃) δ 2.35 (s; 3H); 2.85 (d; 3H); 3.08 (dd; 1H); 3.25 (dd; 1H); 3.39 (dd; 1H); 6.88 - 7.29 (arom.; 3H)

10 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) carbamic acid tert butylester.

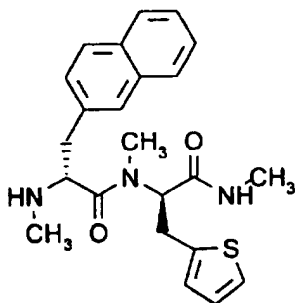
15 2-(tert Butoxycarbonylmethylamino)-3-(2-naphthyl) propionic acid (1.20 g ; 3.55 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxy-7-azabenzotriazol (0.48 g ; 3.55 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.75 g ; 3.90 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.

20 (2R)-N-Methyl-2-methylamino-3-(thiophen-2-yl)propionamide (0.70 g; 3.55 mmol) was dissolved in methylene chloride (10 ml) and added. Diisopropylamine (0.61 ml ; 3.55 mmol) was added. The reaction mixture was stirred at room temperature for 2 days. Methylene chloride (10 ml) and water (10 ml) were added to the reaction mixture. The phases were separated and the
25 organic phase was washed with aqueous sodium hydrogensulfate (10%; 20 ml), saturated aqueous sodium hydrogencarbonate (20 ml). The organic phase was dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was chromatographed on silica (2 x 20 cm) using ethylacetate/heptane (1:1) as eluent to afford 1.38 g of

30 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) carbamic acid tert butylester.

¹H-NMR : (CDCl₃)(selected peaks for major rotamer) d 1.33 (s, 9H); 2.27 (d, 3H); 2.81 (s, 3H); 2.95 (s, 3H); 5.02 (dd; 1H); 5.22 (dd, 1H).

- 5 (2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)-3-(2-naphthyl)propionamide



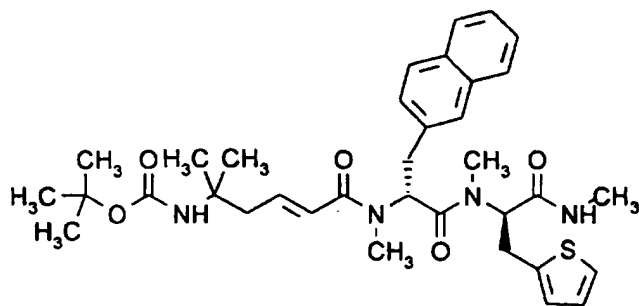
- 10 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl) carbamic acid tert butylester (1.38 g ; 2.71 mmol) was dissolved in methylene chloride (6 ml) and trifluoroacetic acid (4 ml) was added. The reaction mixture was stirred for 1 hour at room temperature. Water (30 ml) and solid sodium hydrogencarbonate were added to pH 8. The
- 15 phases were separated and the aqueous phase was extracted with methylene chloride (4 x 20 ml). The organic phase was dried over magnesium sulfate and the solvent was removed over vacuo to afford 1.06 g of (2R)-N-methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)-3-(2-naphthyl)propionamide.

20

¹H - NMR : (CDCl₃) (selected peaks for major rotamer) d 1.95 (s, 3H); 2.28 (d, 3H); 2.55 (s, 3H); 3.90 (dd, 1H); 5.42 (dd, 1H).

- 25 ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carba

mic acid tert butylester.



5

(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.30 g ; 1.22 mmol) was dissolved in methylene chloride (10 ml). 1-Hydroxy-7-azabenzotiazole (0.17 g ; 1.22 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.26 g ; 1.34 mmol) were added. The reaction mixture was stirred for 15 min at room temperature.

(2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)-3-(2-naphthyl)propionamide (0.50 g ; 1.22 mmol) in methylene chloride (10 ml) was added to the reaction mixture. Diisopropylamine (0.21 ml; 1.22 mmol) was added. The reaction mixture was stirred 12 hours at room temperature. Water (10 ml) and methylene chloride (10 ml) were added. The phases were separated and the organic phase was washed with aqueous sodium hydrogensulfate (10%; 20 ml), saturated aqueous sodium hydrogencarbonate (20 ml), dried over magnesium sulfate and the solvent was removed in vacuo. The crude product was chromatographed on silica (2 x 20 cm) using ethyl acetate/methylene chloride (1:1) as eluent to afford 0.66 g of

((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert butylester.

25

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-

2-(thiophen-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamoyl acid tert butylester (0.66g; 1.04 mmol) was dissolved in methylene chloride (3 ml) and trifluoroacetic acid (2 ml) was added. The reaction mixture was stirred 5 min at room temperature. Water (2 ml) and solid sodium hydrogencarbonate was added to pH 8. The phases were separated and the aqueous phase was extracted with methylene chloride (4 x 15 ml). The organic phase was dried over magnesium sulfate and the solvent was removed in vacuo to afford 0.53 g of the title compound.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ 2.31 (d, 3H); 2.63 (s, 3H); 2.91 (s, 3H); 5.18 (dd, 1H); 5.55 (dd, 1H); 6.19 (d, 1H).

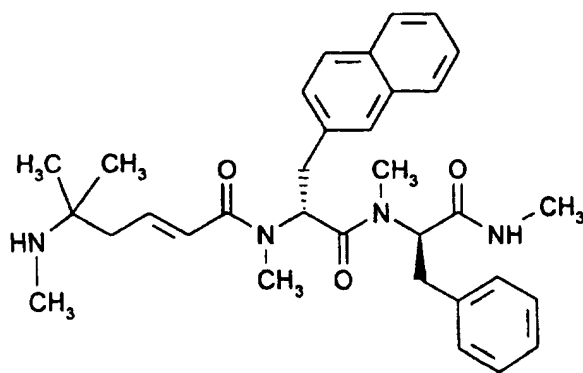
HPLC : t_r = 30.3 min (A1).

PDMS : m/z 534.8 (M+H)⁺

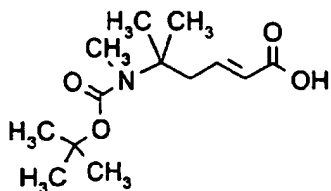
Example 63

(2E)-5-Methyl-5-methylaminohept-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide



(2E)-5-(N-(tert Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid.



5

(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (5.00 g ; 20.6 mmol) was dissolved in tetrahydrofuran (70 ml). Methyl iodide (10.3 ml; 164 mmol) was added and the solution was cooled to 0° C. Sodium hydride (60% in oil)(
 10 2.07 g; 61.6 mmol) was added in portions and the solution was stirred at room temperature for four days. Ethyl acetate (70 ml) and water (60 ml) was added dropwise and the solvent was removed in vacuo. The crude product was dissolved in water (40 ml) and ether (40 ml). The organic phase was washed with a saturated aqueous solution of sodium hydrogencarbonate (30 ml). The aqueous
 15 phases were mixed and 5% aqueous citric acid was added to pH 3. The aqueous phase was extracted with ethylacetate (4 x 50 ml). The organic phase was washed with water (2 x 40 ml), an aqueous solution of sodium thiosulfate (5%; 40 ml), water (40 ml), dried over MgSO₄ and the solvent was removed in vacuo. The residue was dissolved in ethylacetate (45 ml) and washed with an aqueous
 20 solution of sodium hydrogensulfate (10%; 3 x 30 ml), dried over MgSO₄ and and concentrated in vacuo to give 4.00 g of (2E)-5-(N-(tert Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid.

¹H-NMR (CDCl₃) δ 1.38 (s, 6H), 1.45 (s, 9H); 2.80 (d, 2H); 2.85 (s, 3H); 5.88 (d,
 25 1H); 7.01 (q, 1H).

The title compound was prepared analogously to example 1. 5-Methylamino-5-methylhex-2-enoic acid was incorporated instead of 5-amino-5-methylhex-2-enoic

acid.

¹H-NMR : (CDCl₃) (selected peaks for major rotamer) d 1.25 (s, 3H; 1.30 (s, 3H);
5 2.28 (d, 3H); 2.52 (s, 3H); 2.72 (s, 3H); 2.99 (d, 3H); 5.69 (dd, 1H); 5.81 (dd, 1H);
6.13 (d, 1H).

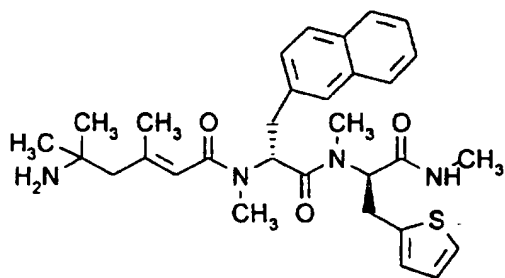
PDMS: m/z 544.4 (M+H)⁺

10 HPLC : t_r = 31.3 min (A1).

Example 64

15 (2E)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl)
)carbamoyl)-2-(2-naphthyl)ethyl) amide.



20

The title compound was prepared analogously to example 1. 2-thienylalanine was
substituted for phenylalanine and 5-amino-3,5-dimethylhex-2-enoic acid was
25 substituted for 5-amino-5-methylhex-2-enoic acid.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 1.24 (s, 3H); 1.25 (s, 3H); 1.76 (s, 2H); 2.32 (s, 3H); 2.76 (d, 3H); 2.99 (s, 3H); 5.65 (dd, 1H); 5.76 (s, 1H); 5.90 (dd, 1H)

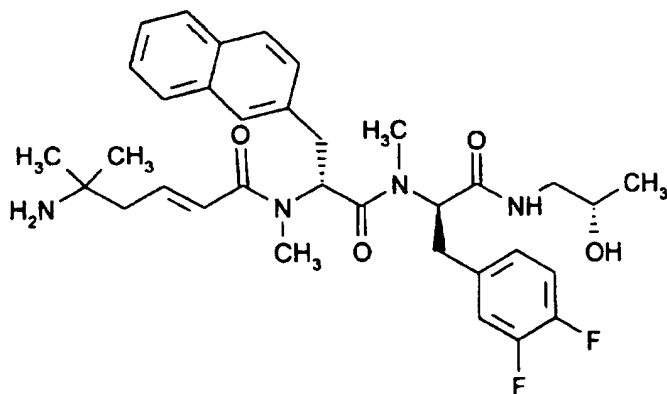
5 HPLC : R_t = 31.45 min.

PDMS : m/z 549.7 (M+H)⁺

10 Example 65

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(3,4-difluorophenyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.

15



This compound was prepared analogously to example 1. 2-(3,4-difluorophenyl)-
20 alanine was substituted for phenylalanine.

¹H-NMR (CDCl₃): (selected peaks for major rotamer) d 1.01 (t, 3H); 1.10 (s, 6H); 2.74 (s, 3H); 3.04 (s, 3H); 5.08 (dd, 1H); 5.56 (dd, 1H); 6.07 (d, 1H).

HPLC : r_t = 32.9 min. (A1)

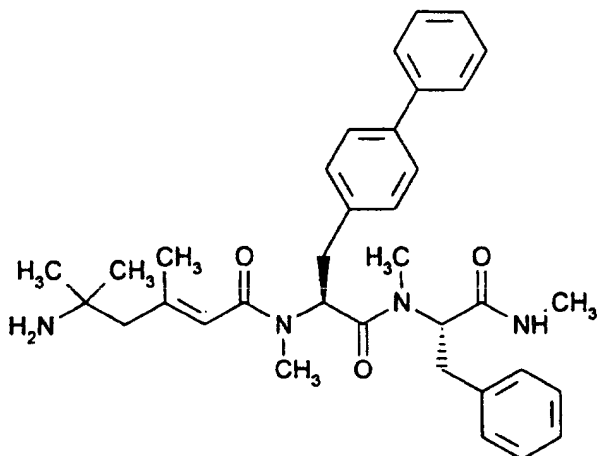
PDMS : m/z 610.3 (M+H)⁺

Example 66

5

5-Amino-3,5-dimethylhex-2-enoic acid

N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide.



10

The title compound was prepared analogously to example 1. N-Tert-Butoxycarbonyl-N-methyl-D-biphenylalanin was substituted for N-tert-

15 butoxycarbonyl-N-methyl-D-phenylalanin in step E.

(2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid was substituted for (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid in step I.

¹H-NMR (CDCl₃) (selected peaks for major rotamer) δ 1.25 (s, 3H); 1.28 (s, 3H);
20 1.57 (s, 3H); 2.32 (s, 3H); 2.73 (d, 3H); 2.94 (s, 3H); 5.34 (dd, 1H); 5.45 (dd, 1H);
5.75 (s, 1H).

HPLC: r_t = 35.37 min (Method A1)

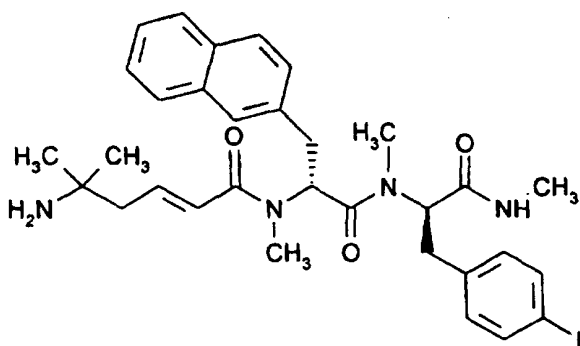
PDMS: $m/z = 569.7$ (M+H)⁺

5 Example 67

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

10



15 This compound was prepared analogously to example 1. N-tert-Butoxycarbonyl-N-methyl-D-4-iodophenylalanine was substituted for N-tert-butoxycarbonyl-N-methyl-D-phenylalanine in step E.

20 ¹H-NMR (CDCl₃)(selected peaks for major rotamer) δ 1.15 (s, 6H); 2.09 (d, 3H); 2.69 (s, 3H); 2.70 (s, 3H); 5.24 (dd, 1H); 5.90 (dd, 1H); 6.18 (d, 1H).

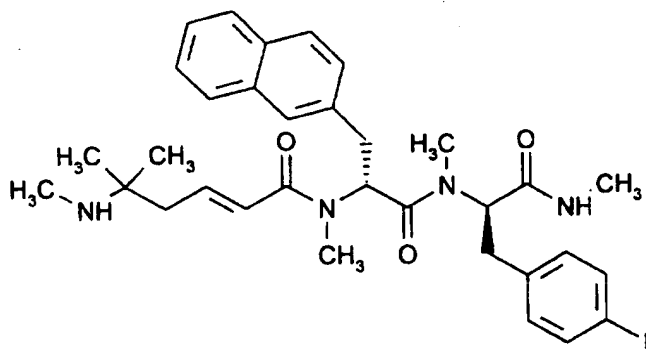
HPLC: $t_r = 35.25$ min (Method A1)

25 PDMS: $m/z = 655.7$ (M+H)⁺

Example 68

5 (2E)-5-Methyl-5-methylaminohex-2-enoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



10

This compound was prepared analogously to example 1. N-Tert-butoxycarbonyl-N-methyl-D-4-iodophenylalanin was substituted for N-tert-butoxycarbonyl-N-methyl-D-phenylalanin in step E. (2E)-5-(N-(tert

15 Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid was substituted for (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid in step I.

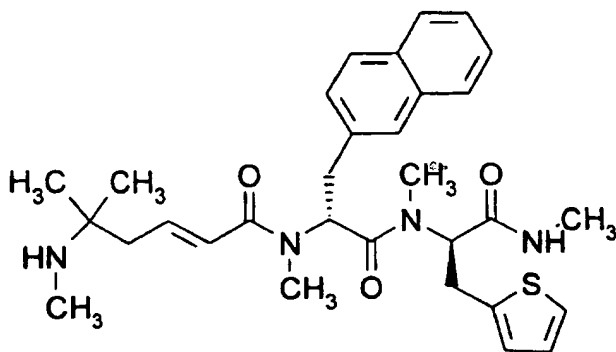
20 ¹H-NMR: (CDCl₃)(selected peaks for major rotamer) d 1.17 (s, 6H); 2.07 (d, 3H); 2.39 (s, 3H); 2.71 (s, 6H); 2.92 (s, 3H); 5.25 (dd, 1H); 5.90 (dd, 1H); 6.20 (d, 1H).

HPLC: *r*_t = 35.38 min (Method A1)

25 PDMS: *m/z* = 668.9 (M+H)⁺

Example 69**(2E) 5-Methyl-5-amino-5-methylhex-2-enoic**

5 **acid-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thien-2-yl)ethyl)**
l)carbamoyl)-2-(2-naphthyl)ethyl)amide.



10

This compound was prepared analogously to example 1. 2-thienyl-alanine was substituted for phenylalanine and 5-methyl-5-methylaminohex-2-enoic acid was substituted for 5-amino-3,5-dimethylhex-2-enoic acid.

15 ¹H-NMR (CDCl₃): (selected peaks for major rotamer) δ 1.25 (s, 3H); 1.28 (s, 3H); 2.26 (d, 3H); 2.68 (s, 3H); 2.95 (s, 3H); 3.06 (s, 3H); 5.25 (dd, 1H); 5.89 (dd, 1H); 6.22 (d, 1H).

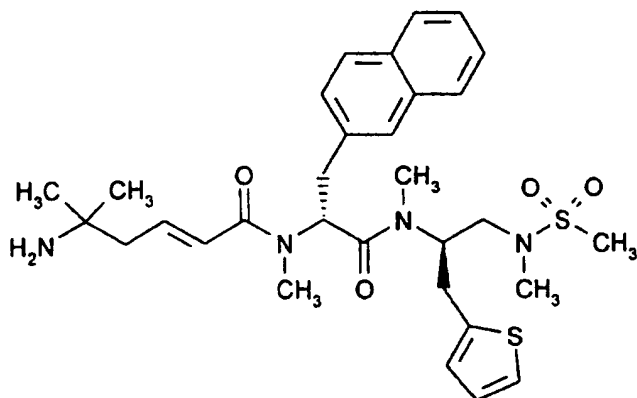
HPLC : t_r = 30.4 min.

20 PDMS : m/z 549.2 (M+H)⁺

Example 70

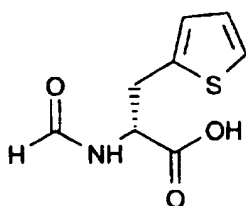
(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-
 25 (methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-

naphthyl)ethyl)hex-2-enamide



5

(2R)-2-(Formylamino)-3-(2-thienyl)propionic acid



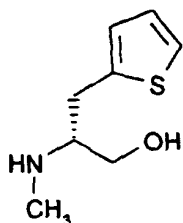
- 10 (2R)-2-Amino-3-(2-thienyl)propionic acid (5.00 g, 29.2 mmol) was dissolved in formic acid (50 ml). The solution was cooled to 0 °C. Acetic acid anhydride (20 ml) was added dropwise. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was cooled to 0 °C. Water (20 ml) was added dropwise. The solution was warmed to room temperature. The solvent was
- 15 removed in vacuo. The residue was suspended in ethyl acetate (20 ml). The precipitation was filtered off, collected, and dried in vacuo, to give 3.60 g of crude (2R)-2-(formylamino)-3-(2-thienyl)propionic acid, which was used for the following step.

- 20 ¹H-NMR (DMSO d₆): δ 3.05 and 3.15 (both ABX, together 1 H); 3.30 and 3.55 (m and ABX, together 1 H); 4.30 and 4.55 (both m, together 1 H); 6.90 (m, 1 H); 6.95

(m, 1 H); 7.35 (d, 1 H); 8.03 (s, 1 H); 8.40 (d, 1 H); 12.92 (br, 1 H).

(2R)-2-Methylamino-3-(2-thienyl)propan-1-ol

5

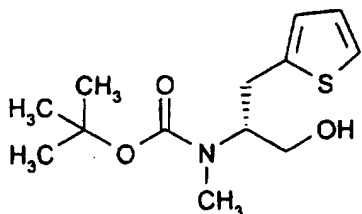


A solution of (2R)-2-(formylamino)-3-(2-thienyl)propionic acid (3.58 g, 18.0 mmol) in tetrahydrofuran (50 ml) was added dropwise to a suspension of sodium
 10 borohydride in tetrahydrofuran (50 ml), which was cooled to 7 - 12 °C (inside temperature). After the addition was finished, a solution of iodine (4.57 g, 18.0 mmol) in tetrahydrofuran (100 ml) was added dropwise. The reaction mixture was heated to reflux for 16 h. It was cooled to 0 °C. Methanol (200 ml) was added dropwise. The solvent was removed in vacuo. The residue was dissolved in a
 15 freshly prepared 20% aqueous sodium hydroxide solution (200 ml). The aqueous phase was extracted with tert-butyl methyl ether (4 x 150 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo to give 3.26 g of crude (2R)-2-methylamino-3-(2-thienyl)propan-1-ol, which was used for the following step.

20

¹H-NMR (DMSO d₆, selected values): d 2.32 (s, 3 H); 2.56 (m, 1 H); 2.84 (m, 2 H); 3,30 (m, 2 H); 6.85 (m, 1 H); 6.93 (m, 1 H); 7.28 (d, 1 H).

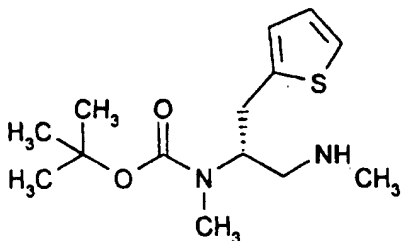
25 N-((1R)-1-(Hydroxymethyl)-2-(2-thienyl)ethyl)-N-methylcarbamic acid tert-butyl ester



A solution of di-tert-butylidicarbonate (4.97 g, 22.8 mmol) in tetrahydrofuran (20
 5 ml) was added dropwise to a solution of (2R)-2-methylamino-3-(2-thienyl)propan-
 1-ol in 1 N aqueous sodium hydroxide solution (19 ml) and tetrahydrofuran (20
 ml). The reaction mixture was stirred at room temperature for 16 h. It was diluted
 with water (100 ml) and extracted with ethyl acetate (3 x 150 ml). The combined
 organic layers were washed with saturated sodium hydrogen carbonate solution
 10 (200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo.
 The crude product was purified by flash chromatography on silica (220 g), using
 ethyl acetate/heptane 1:1 as eluent, to give 3.85 g of N-((1R)-1-(hydroxymethyl)-
 2-(2-thienyl)ethyl)-N-methylcarbamate tert-butyl ester.

15 ¹H-NMR (CDCl₃, selected values) δ 1.41 (br, 9 H); 2.75 (br, 3 H); 3.05 - 3.20 (both
 br, together 2 H); 3.75 (br, 2 H); 4.10 and 4.27 (both br, together 1 H); 6.82 (br, 1
 H); 6.90 (m, 1 H); 7.14 (d, 1 H).

20 N-Methyl-N-((1R)-2-methylamino-1-((2-thienyl)methyl)ethyl)carbamate tert-
 butyl ester



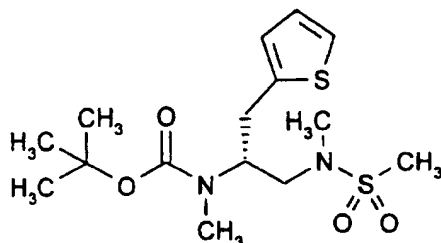
A solution of oxalyl chloride (1.81 ml, 20.8 mmol) in dichloromethane (180 ml) was cooled to -78 °C. A solution of dimethylsulfoxide (2.15 ml, 27.8 mmol) in dichloromethane (2 ml) was added dropwise. The solution was stirred for 15 min at -78 °C. A solution of N-((1R)-1-(hydroxymethyl)-2-(2-thienyl)ethyl)-N-methylcarbamic acid tert-butyl ester (3.78 g, 13.9 mmol) in dichloromethane (10 ml) was added dropwise. The solution was stirred for 20 min at -78 °C. Triethylamine (7.71 ml, 55.6 mmol) was added. The solution was stirred for 5 min at -78 °C and warmed to -35 °C. As soon as -35 °C was reached it was cooled to -78 °C. Acetic acid (3.50 ml, 61.2 mmol) was added. The solution was warmed to room temperature and was washed with brine (200 ml). The organic phase was dried over magnesium sulfate. The solvent was removed in vacuo. The residue was dissolved in methanol (180 ml). 4 Å mol (20 g) sieves was added. Acetic acid (5.5 ml, 97.3 mmol) was added. An 8.0 M solution of methylamine in ethanol (5.2 ml, 41.7 mmol) was added. Solid sodium cyano borohydride (0.57 g, 9.1 mmol) was added. The solution was stirred at room temperature for 1 h, before another portion of solid sodium cyano borohydride (0.57 g, 9.1 mmol) was added. The reaction mixture was stirred for 16 h at room temperature and filtered through a plug of celite. The celite was washed with methanol (150 ml). The solvent of the filtrate was removed in vacuo. The residue was dissolved in 1 N sodium hydroxide solution (200 ml). The solution was extracted with tert-butyl methyl ether (3 x 100 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (150 g), using dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent, to give 1.72 g of N-methyl-N-((1R)-2-methylamino-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values) δ 1.32 and 1.42 (both br, together 9 H); 2.44 (s, 3 H); 2.63 (ABX, 1 H); 2.70 - 2.90 (m, 4 H); 2.95 and 3.03 (both br, together 2 H); 4.40 (br, 1 H); 6.82 (br, 1 H); 6.92 (m, 1 H); 7.15 (d, 1 H).

MS: 285 [M+1]⁺.

N-Methyl-N-((1R)-2-(N-methyl-N-(methylsulfonyl)amino)-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester

5



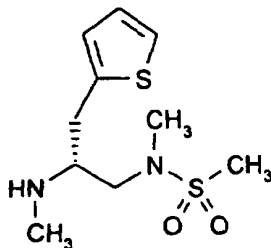
N-Methyl-N-((1R)-2-methylamino-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester (1.72 g, 6.05 mmol) was dissolved in dichloromethane (30 ml).

- 10 Triethylamine (0.84 ml, 6.05 mmol) was added. The solution was cooled to -78 °C. Methanesulfonyl chloride (0.47 ml, 6.05 mmol) was added dropwise. The reaction mixture was warmed to room temperature over a period of 3.5 h. It was stirred at room temperature for 16 h. The reaction mixture was diluted with dichloromethane (100 ml). It was washed with 10% aqueous sodium hydrogen
- 15 sulfate solution (200 ml). The aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (200 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (180 g), using ethyl acetate/heptane 1:1 as eluent, to
- 20 give 1.94 g of N-methyl-N-((1R)-2-(N-methyl-N-(methylsulfonyl)amino)-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃) δ 1.40 and 1.45 (both s, together 9 H); 2.74 and 2.80 (s and m, together 6 H); 2.91 (s, 3 H); 3.06 (m, 3 H); 3.57 (m, 1 H); 4.55 (br, 1 H); 6.85 (d, 1

25 H); 6.92 (m, 1 H); 7.16 (m, 1 H).

N-Methyl-N-((2R)-2-(methylamino)-3-(2-thienyl)propyl)methanesulfonamide

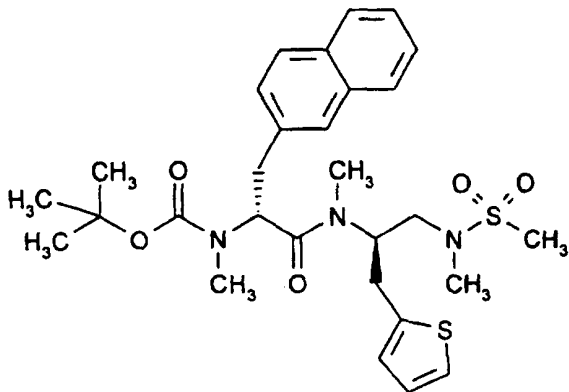


- 5 A solution of of N-methyl-N-((1R)-2-(N-methyl-N-(methanesulfonyl)amino)-1-((2-thienyl)methyl)ethyl)carbamic acid tert-butyl ester (1.87 g, 7.12 mmol) in dichloromethane (7 ml) was cooled to 0 °C. Trifluoroacetic acid (7 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. Dichloromethane (10 ml) was added. A saturated aqueous solution of sodium hydrogen carbonate (10 ml) was
- 10 added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined organic phases were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (120 g),
- 15 using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 1.24 g of N-methyl-N-((2R)-2-(methylamino)-3-(2-thienyl)propyl)methanesulfonamide.

¹H-NMR (CDCl₃) δ 2.47 (s, 3 H); 2.81 (s, 3 H); 2.88 (s, 3 H); 2.90 - 3.10 (m, 4 H); 3.22 (dd, 1 H); 6.86 (m, 1 H); 6.95 (m, 1 H); 7.19 (m, 1 H).

20

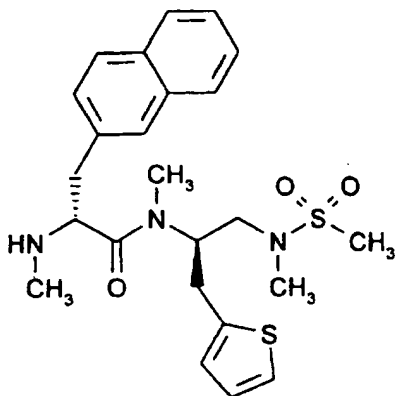
N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methanesulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbonyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester



(2R)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (1.46 g, 4.42 mmol) was dissolved in N,N-dimethylformamide (5 ml) and dichloromethane (5 ml). 1-Hydroxy-7-azabenzotriazole (0.60 g, 4.42 mmol) was added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.85 g, 4.42 mmol) was added. The reaction mixture was stirred for 20 min at 0 °C. A solution of N-methyl-N-((2R)-2-(methylamino)-3-(2-thienyl)propyl)methanesulfonamide (1.16 g, 4.42 mmol) in dichloromethane (5 ml) and ethyldiisopropylamine (0.76 ml, 4.42 mmol) were added successively. The solution was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (90 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (240 g), using ethyl acetate/heptane 2:1 as eluent, to give 2.05 g of N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values) d 1.09 and 1.33 (both s, together 9 H); 5.05 and 5.37 (both dd, together 1 H).

(2R)-2-Methylamino-N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide

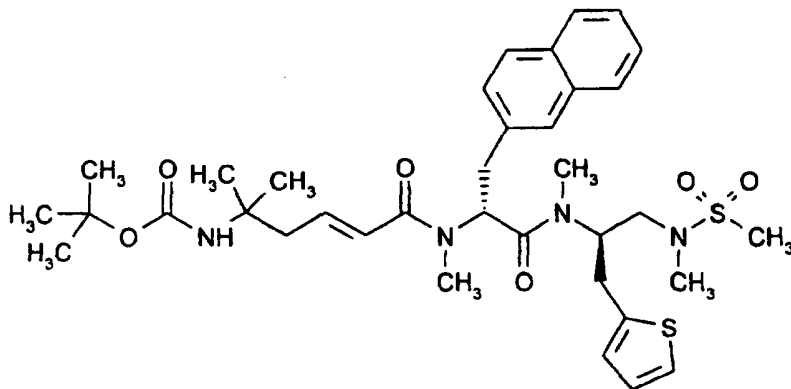


5

A solution of of N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester (1.94 g, 3.37 mmol) in
 10 dichloromethane (7 ml) was cooled to 0 °C. Trifluoroacetic acid (7 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (30 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous solution was extracted
 15 with dichloromethane (2 x 50 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (200 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 1.70 g of
 20 (2R)-2-Methylamino-N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide.

¹H-NMR (CDCl₃, selected values) δ 2.04 and 2.32 (both s, together 3 H); 2.61 and 2.65 (both s, together 3 H); 2.71 and 2.73 (both s, together 3 H); 2.82 and 2.85 (both s, together 3 H); 3.68 and 3.75 (both t, together 1 H); 5.14 (br, 1 H).

5 ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester



(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (158 mg, 0.65 mmol) was dissolved in N,N-dimethylformamide (3 ml) and dichloromethane (3 ml). 1-Hydroxy-7-azabenzotriazole was added. The solution was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (88 mg, 0.65 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C. A solution of (2R)-2-Methylamino-N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide in dichloromethane (3 ml) and ethyldiisopropylamine (0.12 ml, 0.65 mmol) were added successively. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (50 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (50 ml). The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified on silica (120 g), using ethyl acetate/heptane 2:1 (250 ml) and successively ethyl acetate/heptane 3:1 as eluent, to give 282 mg of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-

naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃, selected values) δ 1.15 - 1.35 (m, 6 H); 1.40 and 1.69 (m and br, together 9 H); 5.69 and 5.85 (both m, together 1 H); 6.06, 6.13, and 6.27 (all d, together 1 H).

A solution of ((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(N-methyl-N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester (251 mg, 0.36 mmol) in dichloromethane (3 ml) was cooled to 0 °C. Trifluoroacetic acid (3 ml) was added. The solution was stirred for 50 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (15 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (70 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (3 x 30 ml). The combined organic layers were dried two times over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (120 g), using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 159 mg of the title compound. The HPLC showed a 20% impurity, which is a diastereoisomere of the title compound.

¹H-NMR (CDCl₃, selected values) δ 1.14 (br, 6 H); 5.05 (br, 1 H); 5.66, 5.77, and 5.85 (all dd, together 1 H); 6.08, 6.13 and 6.40 (all dd, together 1 H).

MS 598.8 [M+1]⁺;
599.0 [M+1]⁺, isomeric impurity.

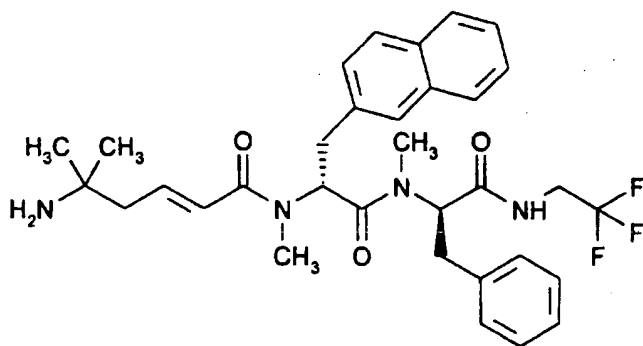
HPLC 31.22 min (A1);
32.75 min (A1, isomeric impurity);
33.18 min (B1);
34.88 min (B1, isomeric impurity).

For biological testing, the title compound was transferred into its acetate salt, by liophilization from 0.5 M acetic acid (50 ml).

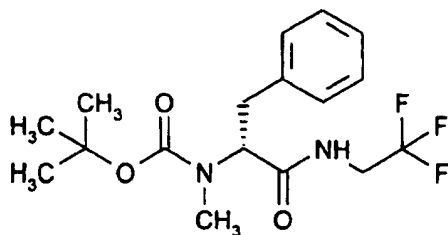
5

Example 71

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-
10 trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide



N-Methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamic acid
15 tert-butyl ester



At 0 °C, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (2.18 g,
20 11.4 mmol) was added to a solution of (2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-phenylpropionic acid (3.0 g, 11.4 mmol) and 1-hydroxybenzotriazole hydrate (1.54 g, 11.4 mmol) in N,N-dimethylformamide (2

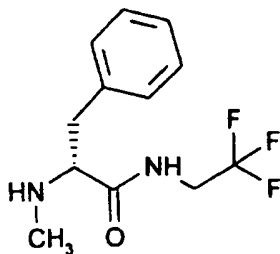
ml) and dichloromethane (4 ml). The reaction mixture was stirred for 15 min at 0 °C. 2,2,2-Trifluoroethylamine (0.91 ml, 11.4 mmol) and ethyldiisopropylamine (2.0 ml, 11.39 mmol) were added successively. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate
5 (150 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (200 ml). The aqueous phase was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (150 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (240 g),
10 using ethyl acetate/heptane 1:2 as eluent, to give 3.52 g of N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamic acid tert-butyl ester.

¹H-NMR (CDCl₃): d 1.30 and 1.42 (both br, together 9 H); 2.76 (s, 3 H); 3.04 (m, 1 H); 3.35 and 3.48 (both m, together 1 H); 3.65 and 3.85 (both m, together 1 H);
15 4.13 (m, 1 H); 4.74 and 4.92 (both br, together 1 H); 5.25 and 6.75 (both br, together 1 H); 7.10 - 7.40 (m, 5 H).

MS: 361.0 [M+1]⁺; 261.0 [M+1-BOC]⁺.

20

(2R)-2-Methylamino-3-phenyl-N-(2,2,2-trifluoroethyl)propionamide



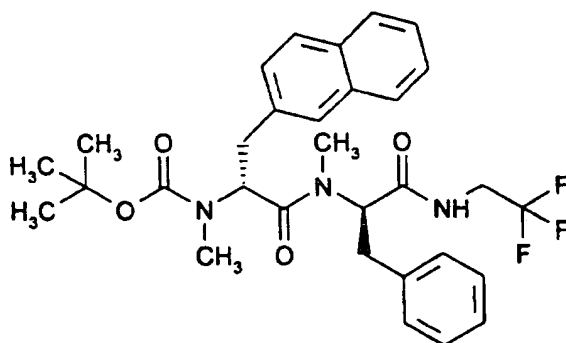
25 N-Methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamic acid tert-butyl ester (3.45 g, 9.57 mmol) was dissolved in dichloromethane (8 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (8 ml) was added. The reaction

mixture was stirred for 45 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (40 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with
 5 dichloromethane (3 x 30 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (180 g), using dichloromethane/methanol/25% aqueous ammonia as eluent to give 1.13 g of (2R)-2-methylamino-3-phenyl-N-(2,2,2-trifluoroethyl)propionamide.

10

¹H-NMR (CDCl₃): d 2.27 (s, 3 H); 2.73 (dd, 1 H); 3.15 - 3.35 (m, 2 H); 3.95 (m, 2 H); 7.15 - 7.40 (m, 5 H); 7.70 (br, 1 H).

15 N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester



20

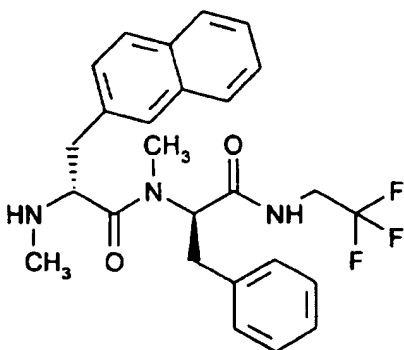
A solution of (2R)-2-(N-(tert-butoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid (1.35 g, 4.1 mmol) and 1-hydroxy-7-azabenzotriazole (0.56 g, 4.1 mmol) in N,N-dimethylformamide (5 ml) and dichloromethane (5 ml) was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide

25 hydrochloride (0.79 g, 4.1 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C. A solution of (2R)-2-methylamino-3-phenyl-N-(2,2,2-

trifluoroethyl)propionamide (1.07 g, 4.1 mmol) in dichloromethane (5 ml) was added. Ethyldiisopropylamine (0.71 ml) was added. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (100 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (100 ml). The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (170 g), using ethyl acetate/heptane 1:2 (300 ml), and then ethyl acetate/heptane/dichloromethane 1:1:1 as eluent to give 1.14 g of N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-butyl ester.

15 ¹H-NMR (CDCl₃, selected values): d 1.09 and 1.31 (both s, together 9 H); 5.00 - 5.50 (m, together 2 H); 7.00 - 7.80 (m, 12 H).

(2R)-2-Methylamino-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((2,2,2-
20 trifluoroethyl)carbamoyl)ethyl)propionamide



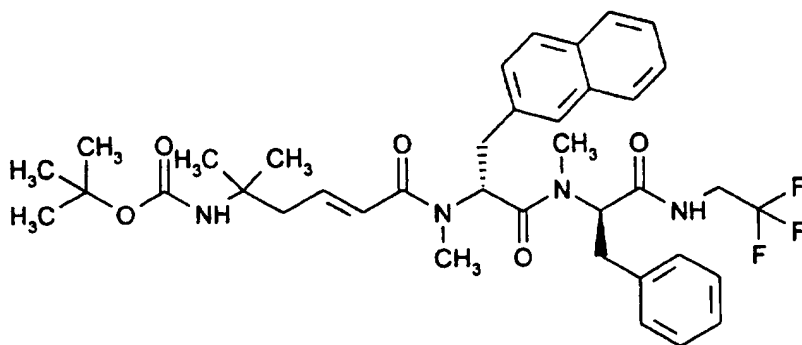
N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-

25 trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamic acid tert-

butyl ester (1.12 g, 1.97 mmol) was dissolved in dichloromethane (6 ml). The solution was cooled to 0 °C. Trifluoroacetic acid (6 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. A saturated solution of aqueous sodium hydrogen carbonate (30 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added until a clear solution was obtained. The phases were separated. The aqueous solution was extracted with dichloromethane (2 x 50 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (90 g), using dichloromethane/methanol/25% aqueous ammonia 100:10:1 as eluent, to give 946 mg of (2R)-2-methylamino-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)propionamide.

¹H-NMR (CDCl₃, selected values): d 1.77, 2.36, 2.65, and 2.91 (all s, together 6 H); 4.56 and 5.55 (both dd, together 1 H); 6.85 - 7.90 (m, together 12 H).

((3E)-4-(N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester



(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid (168 mg, 0.69 mmol) and 1-hydroxy-7-azabenzotriazole (94 mg, 0.69 mmol) were dissolved in N,N-dimethylformamide (3 ml) and dichloromethane (3 ml). The solution was cooled to

0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (132 mg, 0.69 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C. A solution of (2R)-2-methylamino-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)propionamide (327 mg, 0.69 mmol) in
5 dichloromethane (3 ml) was added. Ethyldiisopropylamine (0.12 ml, 0.69 mmol) was added. The reaction mixture was stirred for 16 h, while it was warming up to room temperature. It was diluted with ethyl acetate (50 ml) and washed with 10% aqueous sodium hydrogen sulfate solution (50 ml). The aqueous phase was extracted with ethyl acetate (2 x 20 ml). The combined organic layers were
10 washed with saturated sodium hydrogen carbonate solution (100 ml) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by flash chromatography on silica (160 g), using ethyl acetate/heptane 1:1 as eluent to give 447 mg of ((3E)-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.
15

¹H-NMR (CDCl₃, selected values): δ 1.20, 1.23, 1.28, and 1.29 (all s, together 15 H); 2.55, 2.76, 2.95, and 3.02 (all s, together 6 H); 7.00 - 7.85 (m, 12 H).

20

((3E)-4-(N-Methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester (407 mg, 0.58 mmol) was dissolved in dichloromethane (4 ml). The solution was cooled to 0 °C.
25 Trifluoroacetic acid (4 ml) was added. The reaction mixture was stirred for 45 min at 0 °C. A saturated aqueous solution of sodium hydrogen carbonate (5 ml) was added. Solid sodium hydrogen carbonate was added until pH 7. Water (100 ml) was added, until a clear solution was obtained. The phases were separated. The aqueous phase was extracted with dichloromethane (2 x 20 ml). The combined
30 organic layers were dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified on silica (90 g) using dichloromethane/methanol/25% aqueous ammonia as eluent, to give 251 mg of

the title compound.

¹H-NMR (CDCl₃, selected values): d 1.00 and 1.13 (both s, together 6 H); 2.57, 2.77, 2.98, and 3.06 (all s, together 6 H); 5.30 (m, 1 H); 5.60 and 5.87 (both dd, together 1 H); 6.04 and 6.05 (both d, together 1 H); 6.86 (m, 1 H).

MS: 597.0 [M+1]⁺

HPLC: 35.55 min (A1)

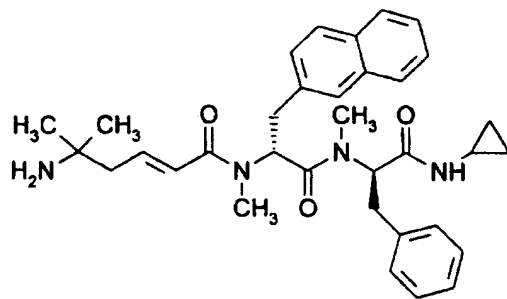
37.87 min (B1).

For biological testing, the title compound was transferred into its acetate salt by liophilization from 0.5 M acetic acid (50 ml).

Example 72

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



This compound was prepared analogously to example 1 using cyclopropylamine instead of methylamine.

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) d 0.43 (m, 4H); 1.08 (s, 6H); 2.99 (s, 3H); 5.15 (dd, 1H); 5.57 (dd, 1H); 6.04 (d, 1H).

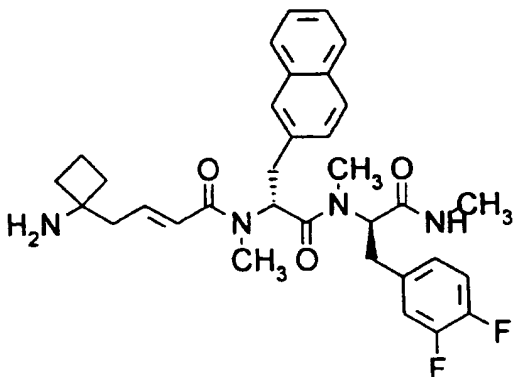
HPLC: $r_t = 33.2$ min (A1)

PDMS: m/z 554 (M+H)⁺

5

Example 73

- 10 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-2-(3,4-difluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



- This compound was prepared analogously to example 1 using (3,4-difluorophenyl)alanine instead of phenylalanine and (2E)-4-(1-(tert-butoxycarbonylamino)cyclobutyl)but-2-enoic acid (prepared as in R. Graf, Org Synth. 46, 51 (1966)) instead of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid.

- 20 ¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.93 (s, 6H); 2.05 (s, 3H); 2.75 (s, 3H); 2.91 (s, 3H); 5.24 (dd, 1H); 5.92 (dd, 1H); 6.29 (d, 1H)

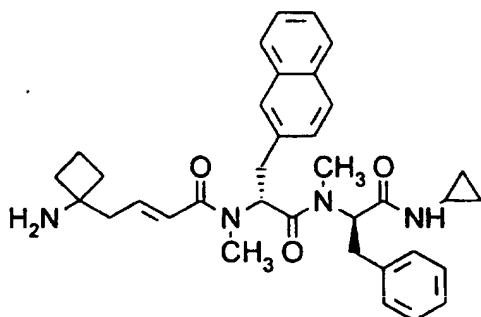
HPLC: $r_t = 33.9$ min (A1)

PDMS: m/z 576 (M+H)⁺

Example 74

5

(2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



10

This compound was prepared analogously to example 1 using cycpropylamine instead of methylamine and and (2E)-4-(1-(tert-butoxycarbonylamino)cyclobutyl)but-2-enoic acid (prepared as in R. Graf, Org Synth. 46, 51 (1966)) instead of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid.

15

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 0.45 (m, 4H); 2.49 (s, 3H); 2.95 (s, 3H); 5.18 (dd, 1H); 5.78 (dd, 3H); 6.33 (d, 1H)

20

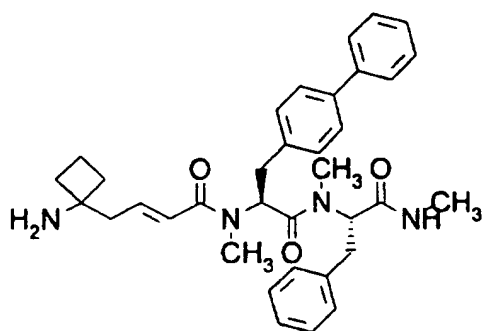
HPLC: t_r = 33.9 min (A1)

PDMS: m/z 567 (M+H)⁺

25

Example 75

(2E) 4-(1-Aminocyclobutyl)-but-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-
 5 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide



This compound was prepared analogously to example 1 using biphenylalanine
 10 instead of phenylalanine and and (2E)-4-(1-(tert-butoxycarbonylamino)cyclobutyl)but-2-enoic acid (prepared as in R. Graf, Org Synth. 46, 51 (1966)) instead of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid.

15

¹H-NMR: (CDCl₃) (selected peaks for major rotamer) δ 1.98 (m, 6H); 2.49 (s, 3H); 2.59 (d, 3H); 2.95 (s, 3H); 5.50 (dd, 1H); 5.78 (dd, 1H); 6.18 (d, 1H).

HPLC: *t_r* = 34.9 min (A1)

20

PDMS: *m/z* (M+H)⁺

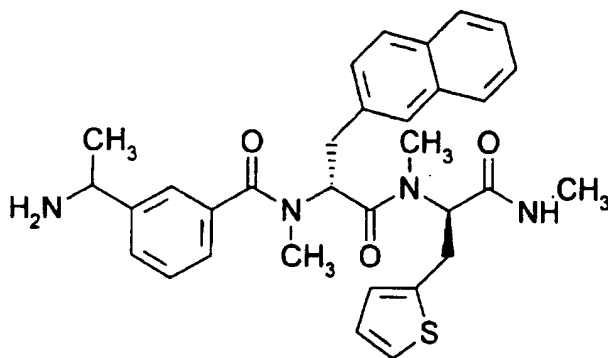
LC-MS: 569.0 (m+1)⁺

25

Example 76

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide

5



The N-Methyl-PAL-Resin (75 mg, 0.045 mmol, load: 0.60) was washed with
 10 5 % diisopropylethylamine in dichloromethane (2 x 2 mL), dichloromethane
 (3 x 2 mL) and dimethylformamide (3 x 2 mL) and then swelled in
 dimethylformamide (2 mL). Then 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid (46 mg, 0.09 mmol) in
 dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-
 15 tetramethyluronium hexafluorophosphate (34 mg, 0.09 mmol) in
 dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (15 mg, 0.09
 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (31 mL, 0.18
 mmol) in dimethylformamide (1 mL) were added and the mixture was
 shaken overnight. The resin was filtered and washed with
 20 dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and
 dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5
 mL) was added and the mixture was shaken for 20 min, filtered and washed
 with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and
 dimethylformamide (2 mL). Then 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-
 25 methylamino)-3-(2-naphthyl)propionic acid (41 mg, 0.09 mmol) in

dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (34 mg, 0.09 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (15 mg, 0.09 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (31 mL, 0.18 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 20 % piperidine in dimethylformamide (5 mL) was added and the mixture was shaken for 20 min, filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). Then 3-(1-(tert-butoxycarbonylamino)ethyl)-benzoic acid (22 mg, 0.09 mmol) in dimethylformamide (1 mL), O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (34 mg, 0.09 mmol) in dimethylformamide (1 mL), 1-hydroxy-7-azabenzotriazole (15 mg, 0.09 mmol) in dimethylformamide (1 mL) and diisopropylethylamine (31 mL, 0.18 mmol) in dimethylformamide (1 mL) were added and the mixture was shaken overnight. The resin was filtered and washed with dimethylformamide (3 x 2 mL), dichloromethane (3 x 2 mL) and dimethylformamide (2 mL). The resin was cooled to 0 °C and 50 % trifluoroacetic acid in dichloromethane (4 mL) was added and the mixture was shaken for 10 min at 0 °C. The resin was filtered and washed with 50 % trifluoroacetic acid in dichloromethane (2 x 0.5 mL) and the combined filtrates were concentrated under a stream of nitrogen. The obtained product was dissolved in acetonitrile/water 1:20 (10 mL) and applied to a C-18 Sep-Pak Classic® cartridge (0.25 g, purchased from Waters™), which had been prewashed with acetonitrile (10 mL) and water (10 mL). Then water/trifluoroacetic acid 99.9:0.1 (5 mL), followed by water/acetonitrile/trifluoroacetic acid 89.9:20:0.1 (4 mL) was run through the Sep-Pak® and the filtrate was discarded. Then the Sep-Pak® was washed with water/acetonitrile/trifluoroacetic acid 64.9:35:0.1 (4 mL) and the filtrate was diluted with water (11 mL) and lyophilized to 4 mg of the title product.

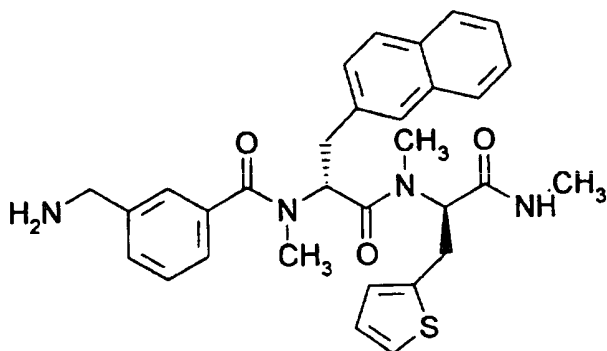
HPLC:(A1) $R_t = 31.05$ min

(B1) $R_t = 33.00$ min

5 LC-MS: 557.0 (m+1)⁺

Example 77

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
10 2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide:



The title compound was prepared analogously to example 76 with 3-(1-(tert-
15 butoxycarbonylamino)methyl)-benzoic acid instead of 3-(1-(tert-butoxy-
carbonylamino)ethyl)benzoic acid.

Yield: 5.0 mg

20 HPLC:(A1) $R_t = 30.32$ min

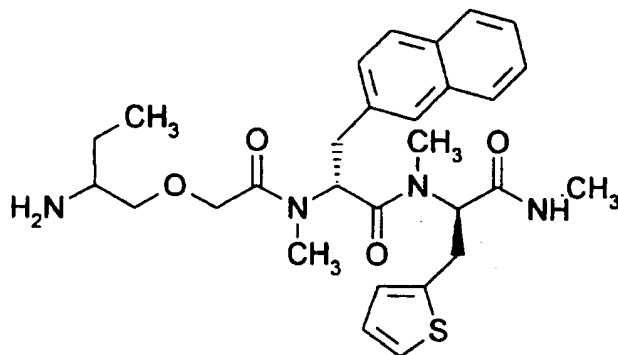
(B1) $R_t = 32.22$ min

LC-MS: 542.8 (m+1)⁺

Example 78

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide:

5



The title compound was prepared analogously to example 76 with (2-(tert-butoxycarbonylamino)butoxy)- acetic acid instead of 3-(1-(tert-butoxy-
10 carbonylamino)ethyl)benzoic acid.

Yield: 10.4 mg

HPLC: (A1) $R_t = 30.13$ min

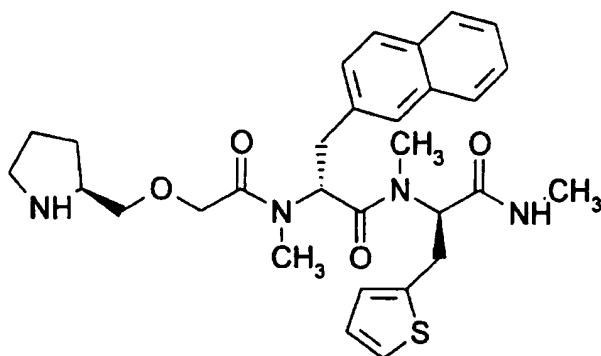
15 (B1) $R_t = 31.98$ min

LC-MS: $(m+1)^+$

Example 79

20

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide:



The title compound was prepared analogously to example 76 with (2S)-2-
 (((carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butyl ester
 5 instead of 3-(1-(tert-butoxy-carbonylamino)ethyl)benzoic acid.

Yield: 9.4 mg

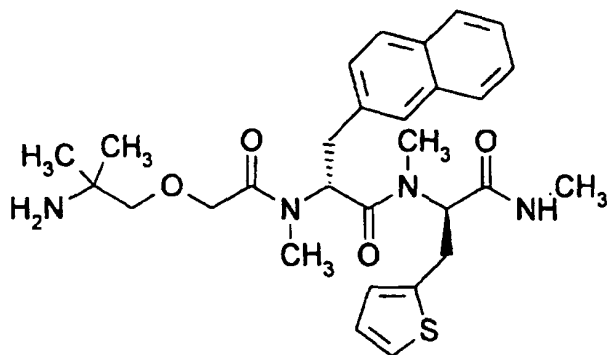
HPLC: (A1) R_t = 30.07 min

10 (B1) R_t = 31.88 min

LC-MS: (m+1)⁺

15 Example 80

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide:



The title compound was prepared analogously to example 76 with (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid instead of 3-(1-(tert-butoxycarbonylamino)ethyl)benzoic acid.

Yield: 10.5 mg

HPLC:(A1) $R_t = 29.77$ min

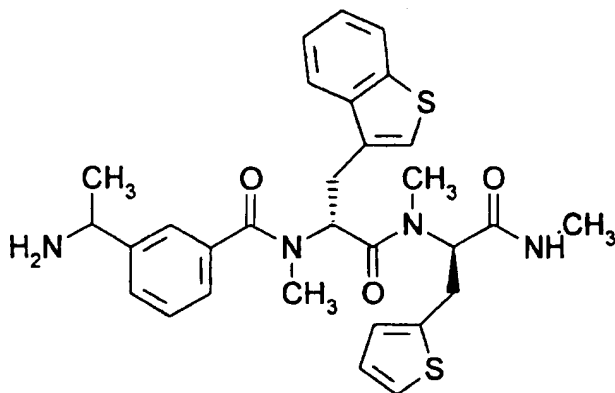
10 (B1) $R_t = 31.62$ min

LC-MS: $(m+1)^+$

15 Example 81

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide:

20



The title compound was prepared analogously to example 76 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 3.2 mg

10 HPLC: (A1) $R_t = 30.62$ min
(B1) $R_t = 32.57$ min

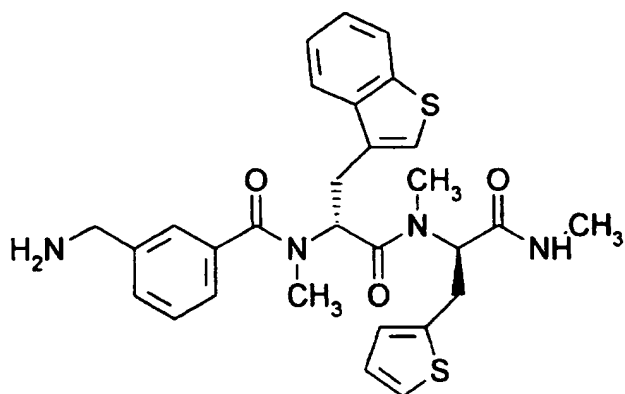
LC-MS: 563.0 (m+1)⁺

15

Example 82

3-(1-Aminomethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 77 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 2.0 mg

HPLC: (A1) $R_t = 29.82$ min
(B1) $R_t = 31.73$ min

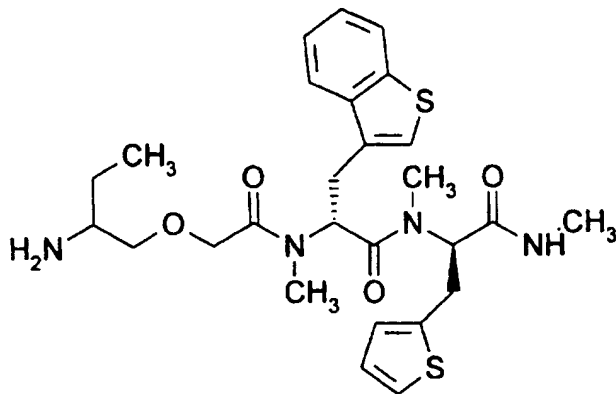
LC-MS: 549.0 ($m+1$)⁺

15

Example 83

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:

20



The title compound was prepared analogously to example 78 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: mg

10 HPLC: (A1) R_t = min
(B1) R_t = min

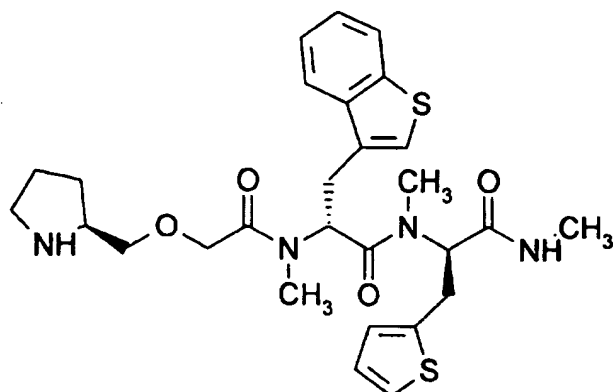
LC-MS: (m+1)⁺

15

Example 84

(2R)-2-(N-((((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide:

20



The title compound was prepared analogously to example 79 with (2R)-3-
 (benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 5 methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-
 yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

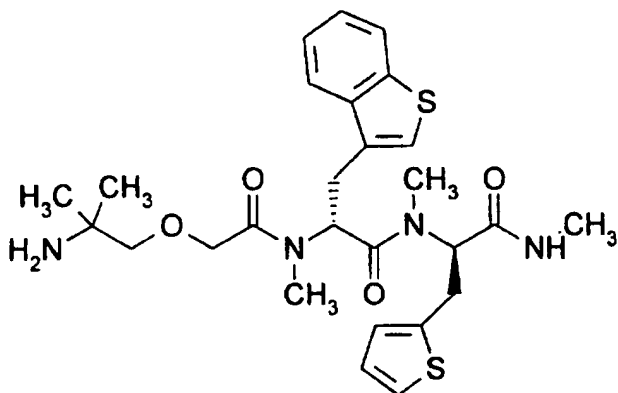
Yield: 7.6 mg

10 HPLC:(A1) $R_t = 29.42$ min
 (B1) $R_t = 31.23$ min

LC-MS: 557.0 (m+1)⁺

15 Example 85

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-
 yl)propionamide:



The title compound was prepared analogously to example 80 with (2R)-3-(benzo[b]thiophen-3-yl)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 5.8 mg

HPLC: (A1) $R_t = 29.22$ min
(B1) $R_t = 31.00$ min

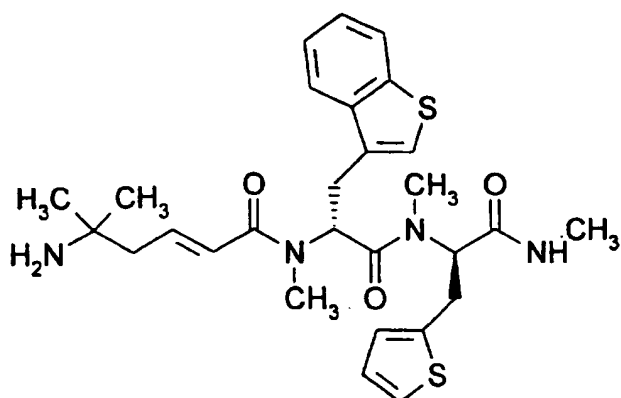
LC-MS: 544.8 (m+1)⁺

15

Example 86

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)amide:

20



The title compound was prepared analogously to example 85 with (2E)-5-
 (tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-
 5 butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 2.0 mg

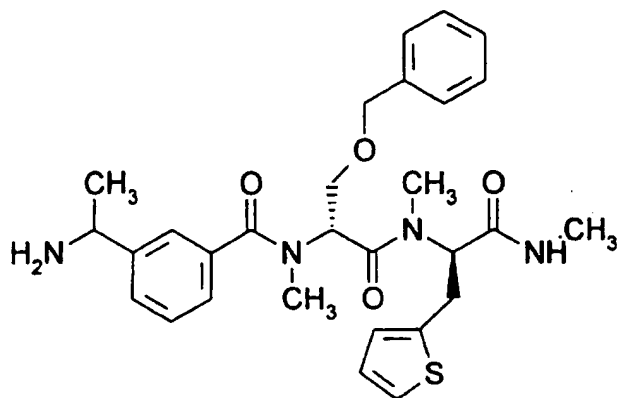
HPLC: (A1) $R_t = 29.62$ min

10 (B1) $R_t = 31.50$ min

LC-MS: 541.2 (m+1)⁺

15 Example 87

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-
 (benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-2-
 ((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic
 5 acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-
 (2-naphthyl)propionic acid.

Yield: 10.0 mg

10 HPLC:(A1) $R_t = 28.85$ min
 (B1) $R_t = 30.67$ min

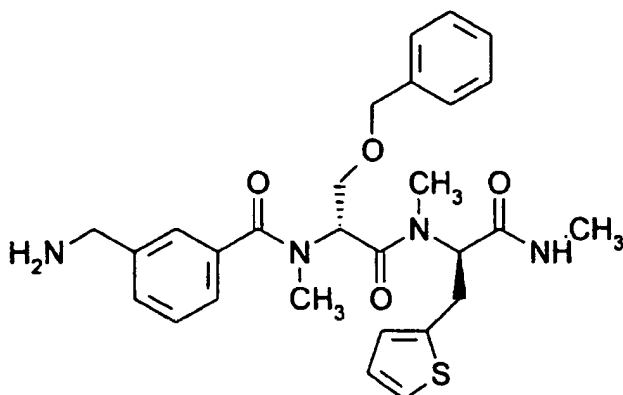
LC-MS: $(m+1)^+$

15

Example 88

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:

20



The title compound was prepared analogously to example 77 with (2R)-2-
 ((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic
 5 acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-
 (2-naphthyl)propionic acid.

Yield: 8.4 mg

10 HPLC:(A1) R_t = 30.45 min
 (B1) R_t = 30.43 min

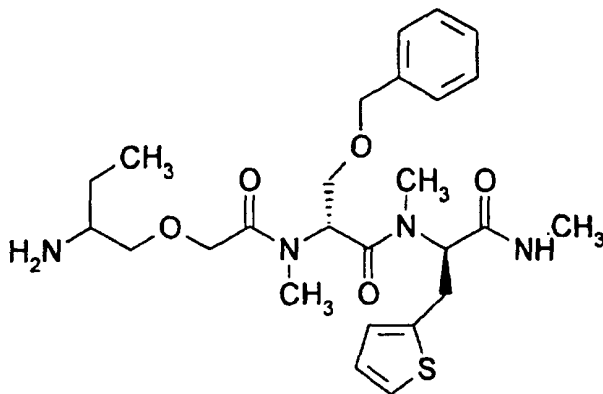
LC-MS: 522.8 (m+1)⁺

15

Example 89

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 78 with (2R)-2-
 ((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic
 5 acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-
 (2-naphthyl)propionic acid.

Yield: 9.8 mg

10 HPLC: (A1) $R_t = \text{min}$
 (B1) $R_t = \text{min}$

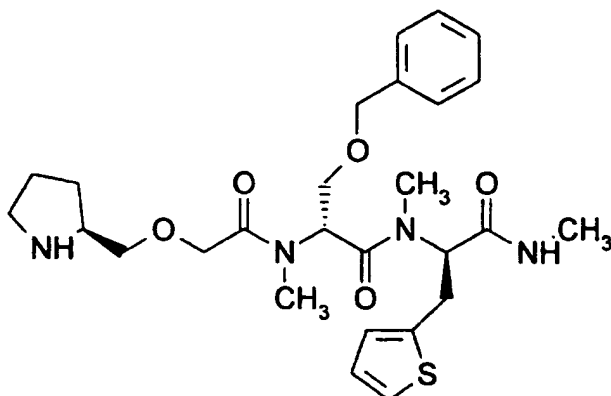
LC-MS: 519.0 (m+1)⁺

15

Example 90

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 79 with (2R)-2-
 ((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic
 5 acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-
 (2-naphthyl)propionic acid.

Yield: 11.1 mg

10 HPLC:(A1) $R_t = 27.77$ min
 (B1) $R_t = 29.40$ min

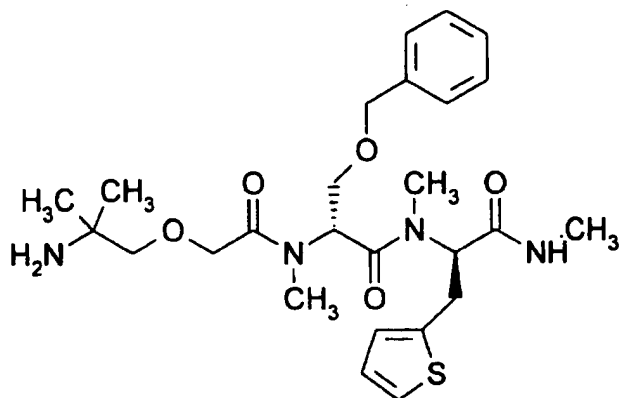
LC-MS: (m+1)⁺

15

Example 91

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 80 with (2R)-2-
 ((9H-fluoren-9-ylmethoxy-carbamoyl)methylamino)- 3-benzyloxypropionic
 5 acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-
 (2-naphthyl)propionic acid.

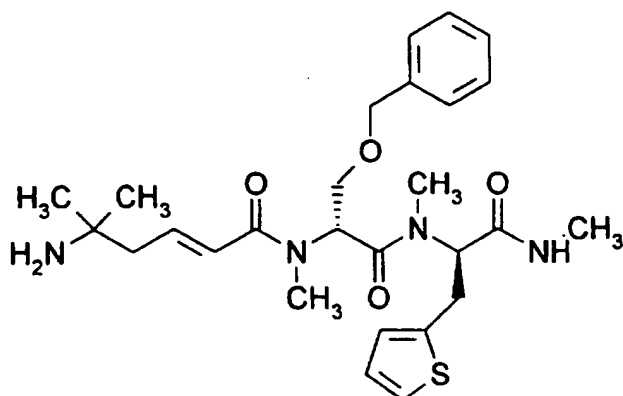
Yield: 11.9 mg

10 HPLC:(A1) $R_t = 28.50$ min
 (B1) $R_t = 29.23$ min

LC-MS: 519.0 (m+1)⁺

15 Example 92

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-
 (benzyloxy)ethyl)amide:



The title compound was prepared analogously to example 91 with (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 1.5 mg

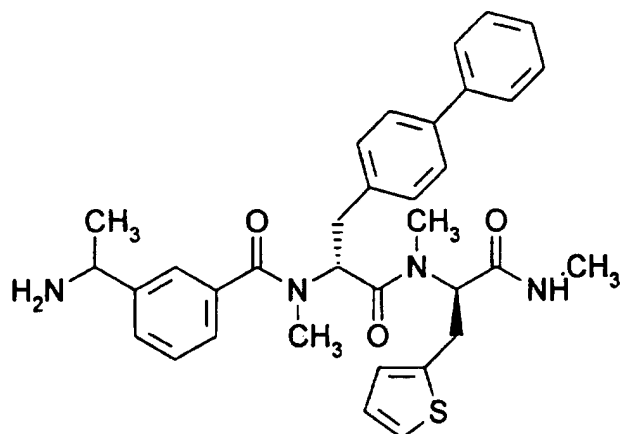
HPLC: (A1) $R_t = 28.03$ min

10 (B1) $R_t = 29.77$ min

LC-MS: $(m+1)^+$

15 Example 93

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-3-
 (biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-
 5 methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 2.0 mg

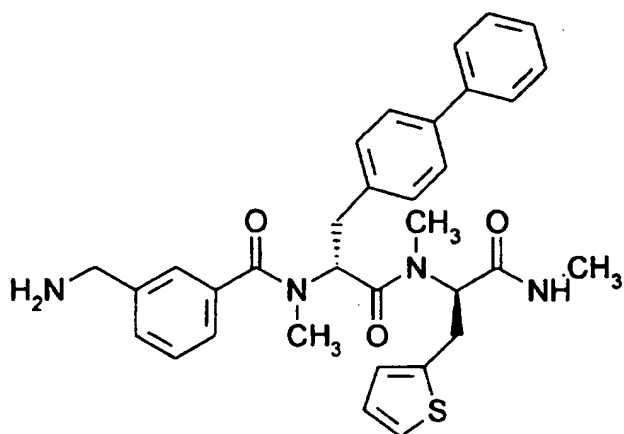
10 HPLC:(A1) $R_t = 34.58$ min
 (B1) $R_t = 36.67$ min

LC-MS: $(m+1)^+$

15 Example 94

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

300



The title compound was prepared analogously to example 77 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

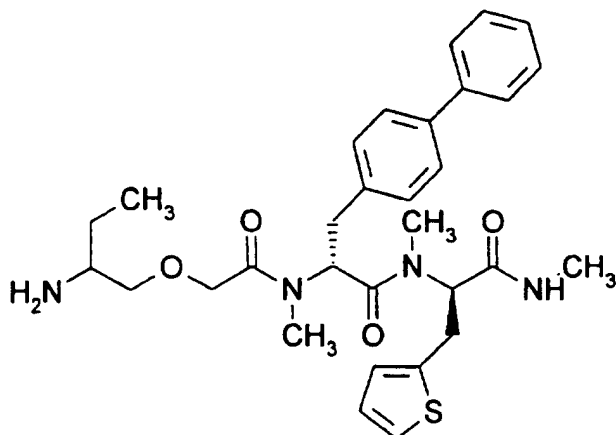
Yield: 12.3 mg

HPLC: (A1) $R_t = 33.92$ min
(B1) $R_t = 35.97$ min

LC-MS: $(m+1)^+$

Example 95

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 78 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 13.5 mg

HPLC:(A1) $R_t = 33.57$ min
(B1) $R_t = 34.47$ min

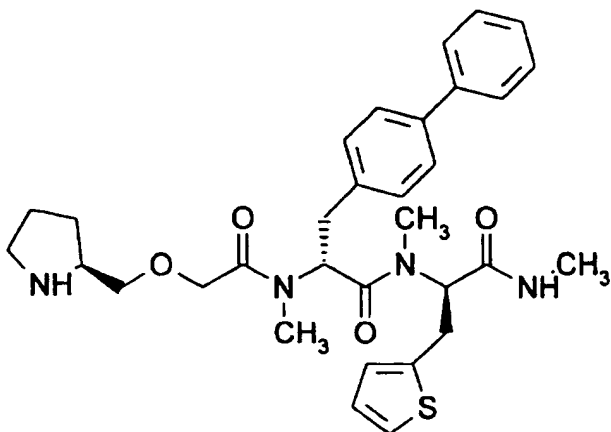
LC-MS: (m+1)⁺

15

Example 96

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 79 with (2R)-3-(biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

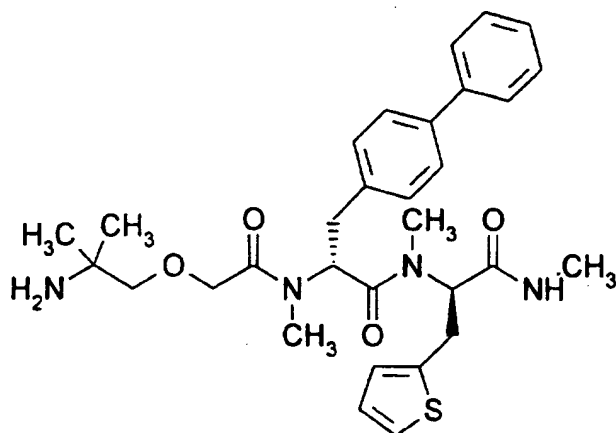
Yield: 11.0 mg

HPLC:(A1) $R_t = 33.30$ min
(B1) $R_t = 35.24$ min

LC-MS: $(m+1)^+$

Example 97

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methoxycarbonyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 80 with (2R)-3-
 (biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-
 5 methylamino)propionic acid instead of 2-(N-((9H-fluoren-9-
 yl)methoxycarbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid.

Yield: 13.1 mg

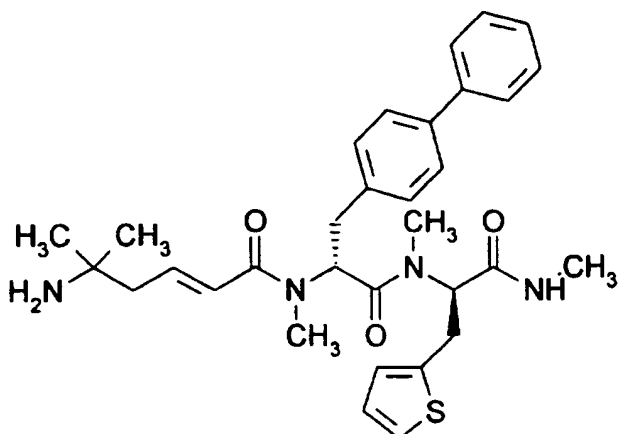
10 HPLC:(A1) R_t = 27.68 min
 (B1) R_t = 30.22 min

LC-MS: (m+1)⁺

15

Example 98

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-
 20 yl)ethyl)amide:



The title compound was prepared analogously to example 97 with (2E)-5-
 (tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-
 5 butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 13.1 mg

HPLC:(A1) $R_t = 28.48$ min

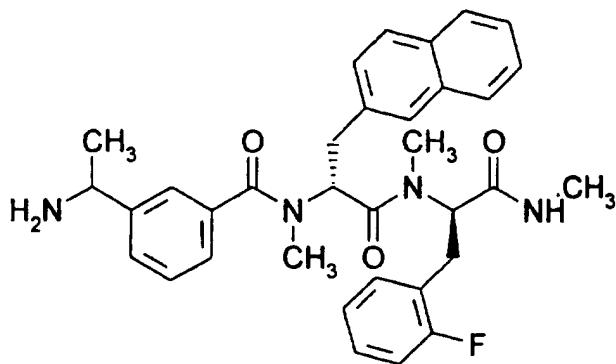
10 (B1) $R_t = 30.03$ min

LC-MS: $(m+1)^+$

15

Example 99

20 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(
 (methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(2-
 naphthyl) thyl)benzamide:



The title compound was prepared analogously to example 76 with (2R)-2-
 (N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 5.0 mg

10

HPLC:(A1) $R_t = 32.00$ min

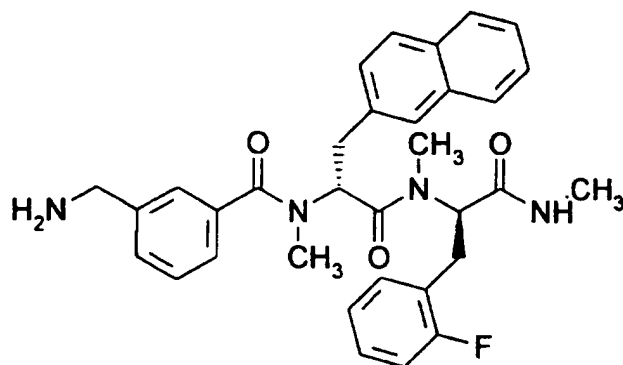
(B1) $R_t = 33.98$ min

LC-MS: 568.8 (m+1)⁺

15

Example 100

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 20 2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide:



The title compound was prepared analogously to example 77 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 2.8 mg

10

HPLC:(A1) $R_t = 31.30$ min

(B1) $R_t = 33.23$ min

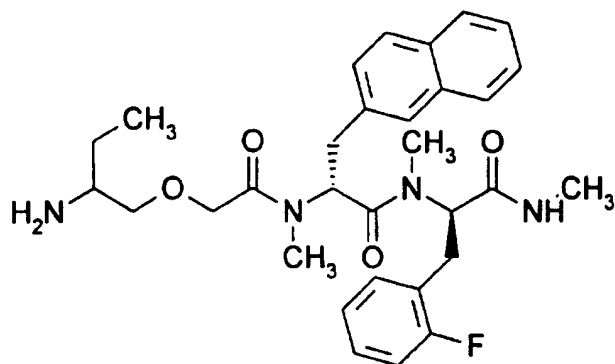
LC-MS: 555.0 (m+1)⁺

15

Example 101

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide:

20



The title compound was prepared analogously to example 78 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 10.1 mg

10

HPLC:(A1) $R_t = 31.25$ min

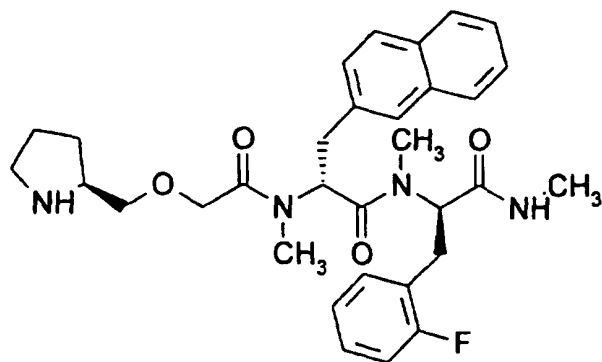
(B1) $R_t = 33.03$ min

LC-MS: $(m+1)^+$

15

Example 102

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propion-
 20 amide:



The title compound was prepared analogously to example 79 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 12.0 mg

10

HPLC:(A1) $R_t = 31.90$ min

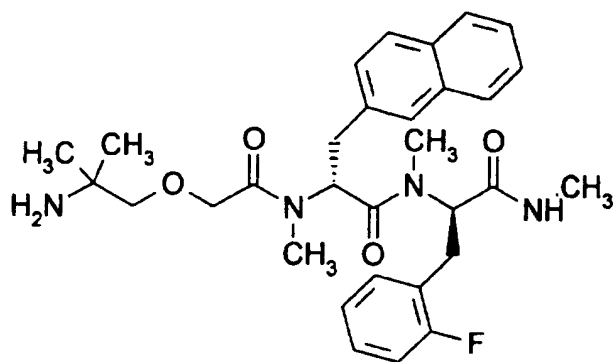
(B1) $R_t = 32.73$ min

LC-MS: 563.0 (m+1)⁺

15

Example 103

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propion-
 20 amide:



The title compound was prepared analogously to example 80 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 11.5 mg

10

HPLC:(A1) $R_t = 30.83$ min

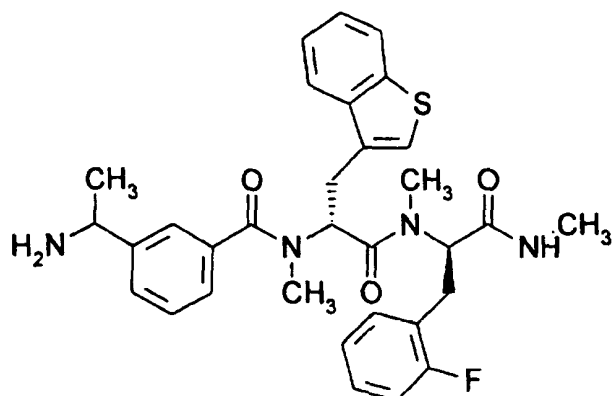
(B1) $R_t = 32.63$ min

LC-MS: 551.0 (m+1)⁺

15

Example 104

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-
 20 3-yl)ethyl)-benzamide:



The title compound was prepared analogously to example 81 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 3.6 mg

10

HPLC:(A1) $R_t = 31.60$ min

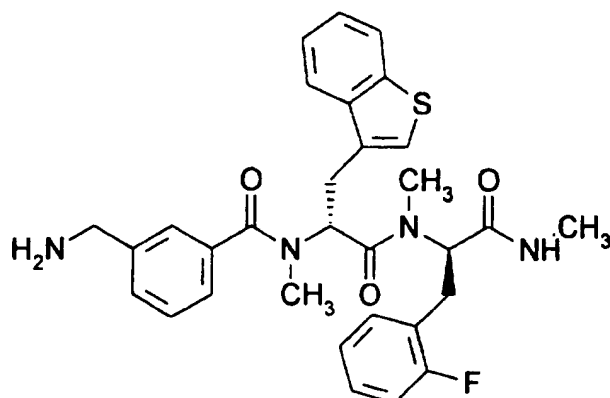
(B1) $R_t = 33.57$ min

LC-MS: 575.0 (m+1)⁺

15

Example 105

20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benz-
 amide:



The title compound was prepared analogously to example 82 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 3.3 mg

10

HPLC: (A1) $R_t = 30.82$ min

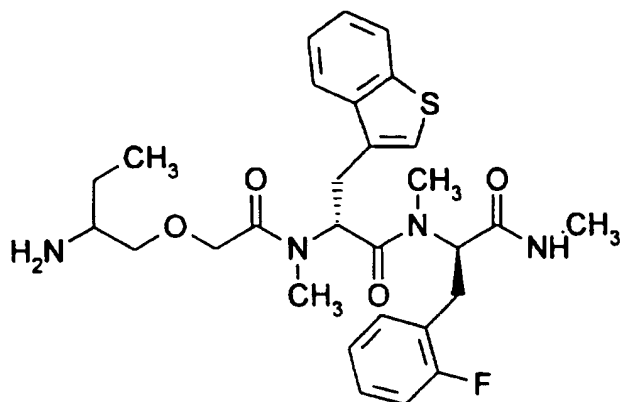
(B1) $R_t = 32.77$ min

LC-MS: 561.0 (m+1)⁺

15

Example 106

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-
 yl)propionamide:



The title compound was prepared analogously to example 83 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 10.5 mg

10

HPLC:(A1) $R_t = 30.62$ min

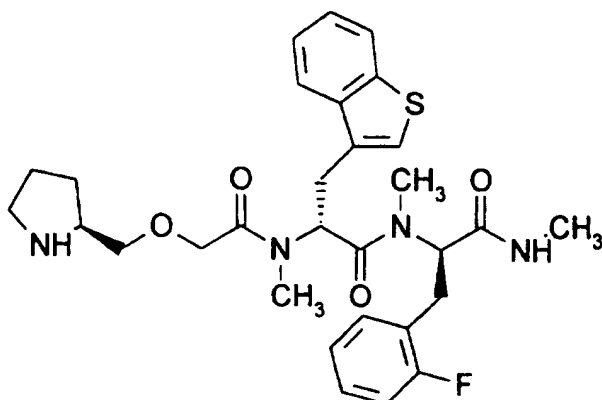
(B1) $R_t = 32.45$ min

LC-MS: 557.0 (m+1)⁺

15

Example 107

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-
 20 yl)propionamide:



The title compound was prepared analogously to example 84 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 7.0 mg

10

HPLC:(A1) $R_t = 30.47$ min

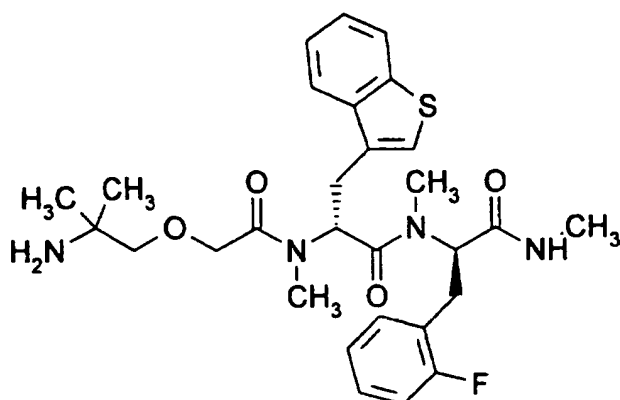
(B1) $R_t = 32.30$ min

LC-MS: 569.0 (m+1)⁺

15

Example 108

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 20 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-
 yl)propionamide:



The title compound was prepared analogously to example 85 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 7.5 mg

10

HPLC:(A1) $R_t = 30.33$ min

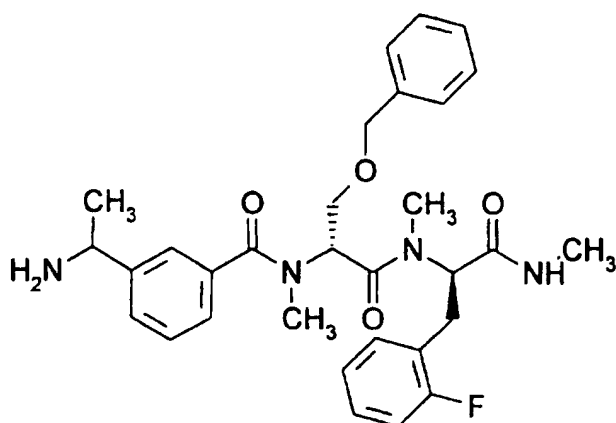
(B1) $R_t = 32.10$ min

LC-MS: 557.0 (m+1)⁺

15

Example 109

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-
 20 (benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 87 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 4.6 mg

10

HPLC:(A1) $R_t = 31.07$ min

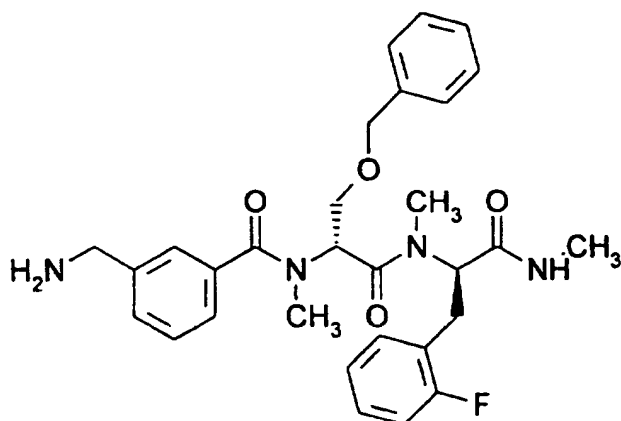
(B1) $R_t = 32.97$ min

LC-MS: 549.0 (m+1)⁺

15

Example 110

20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 88 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 5.2 mg

10

HPLC:(A1) $R_t = 30.25$ min

(B1) $R_t = 32.10$ min

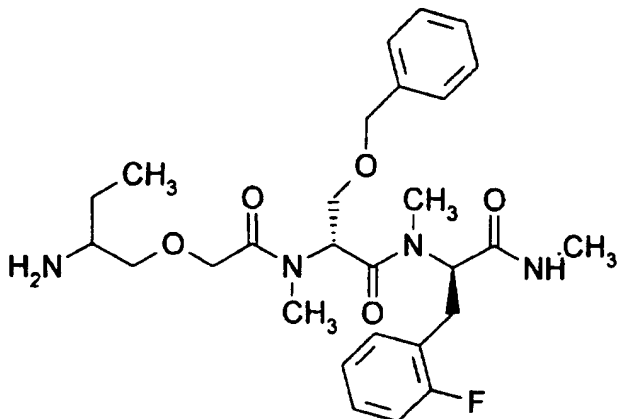
LC-MS: 535.2 ($m+1$)⁺

15

Example 111

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 89 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 23.6 mg

10

HPLC: (A1) $R_t = 29.32$ min

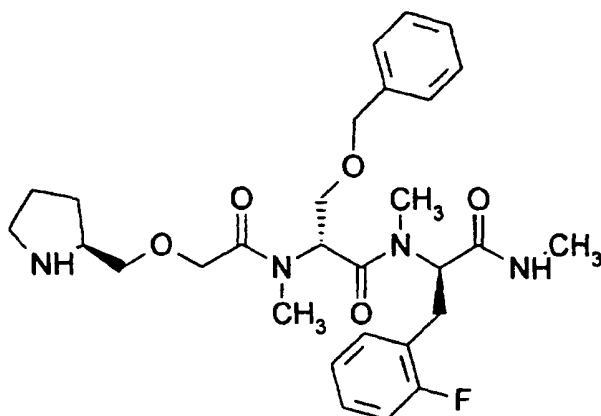
(B1) $R_t = 30.97$ min

LC-MS: $(m+1)^+$

15

Example 112

20 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-
 (benzyloxy)propionamide:



The title compound was prepared analogously to example 90 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 26.0 mg

10

HPLC:(A1) R_t = min

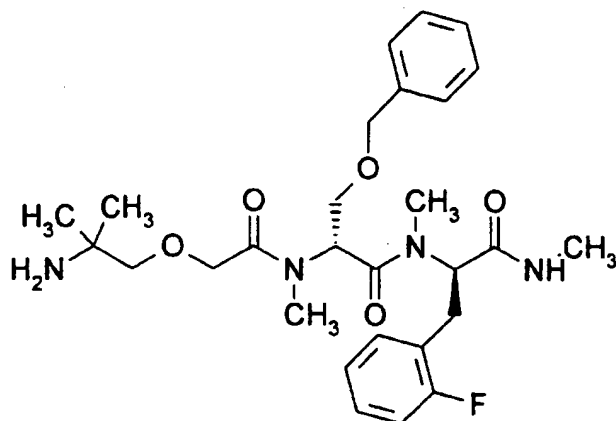
(B1) R_t = min

LC-MS: 543.2 (m+1)⁺

15

Example 113

20 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-
 (benzyloxy)propionamide:



The title compound was prepared analogously to example 91 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 20.1 mg

10

HPLC:(A1) $R_t = 30.17$ min

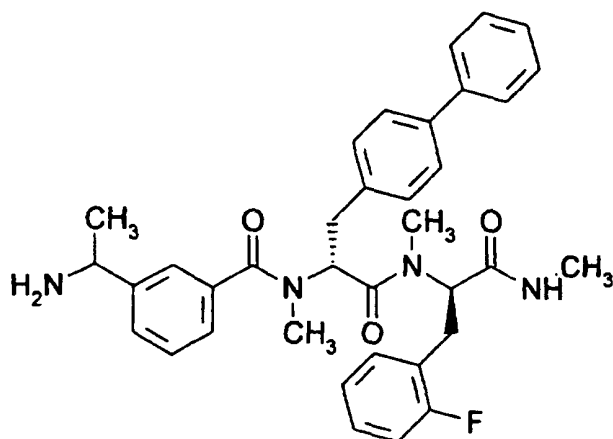
(B1) $R_t = 30.77$ min

LC-MS: 531.0 (m+1)⁺

15

Example 114

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-
 yl)ethyl)benzamide:



The title compound was prepared analogously to example 93 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 10.0 mg

10

HPLC:(A1) $R_t = 35.40$ min

(B1) $R_t = 37.58$ min

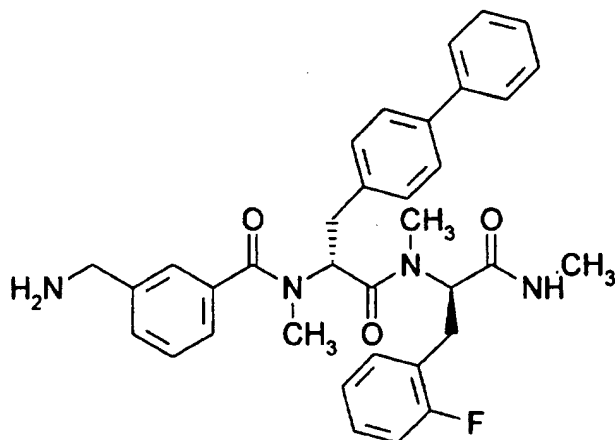
LC-MS: 594.8 (m+1)⁺

15

Example 115

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 94 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 6.6 mg

10

HPLC:(A1) $R_t = 34.70$ min

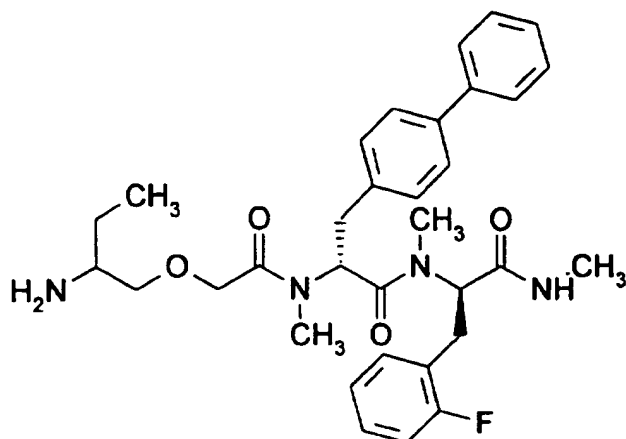
(B1) $R_t = 36.08$ min

LC-MS: 581.0 (m+1)⁺

15

Example 116

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide:



The title compound was prepared analogously to example 95 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 23.3 mg

10

HPLC:(A1) $R_t = 34.13$ min

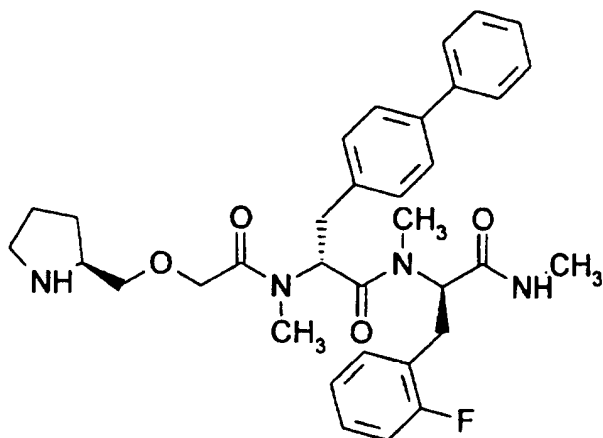
(B1) $R_t = 36.08$ min

LC-MS: $(m+1)^+$

15

Example 117

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-
 20 yl)propionamide:



The title compound was prepared analogously to example 96 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 20.5 mg

10

HPLC:(A1) $R_t = 27.65$ min

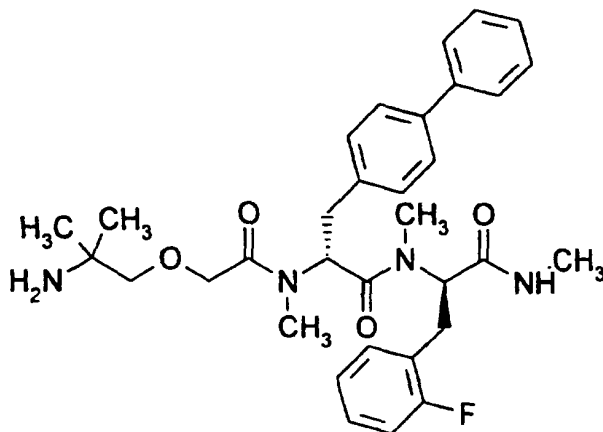
(B1) $R_t = 30.18$ min

LC-MS: (m+1)⁺

15

Example 118

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 20 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-
 yl)propionamide:



The title compound was prepared analogously to example 97 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 12.2 mg

10

HPLC: (A1) $R_t = 34.32$ min

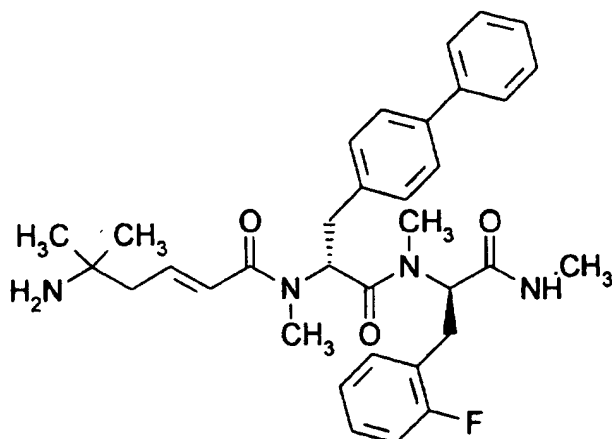
(B1) $R_t = 36.13$ min

LC-MS: 577.0 ($m+1$)⁺

15

Example 119

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(biphenyl-4-
 20 yl)ethyl)amide:



The title compound was prepared analogously to example 98 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(2-fluorophenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)propionic acid.

Yield: 5.1 mg

10

HPLC:(A1) $R_t = 27.68$ min

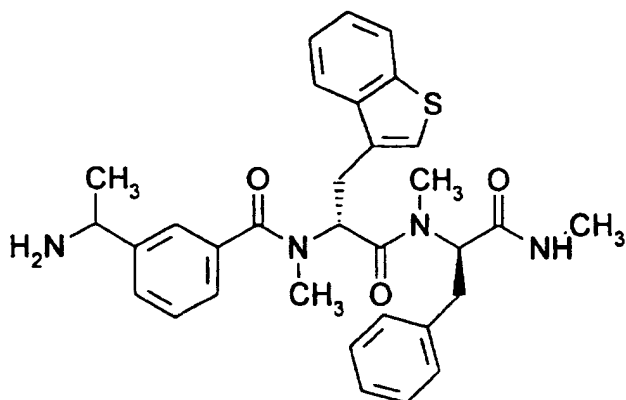
(B1) $R_t = 30.20$ min

LC-MS: $(m+1)^+$

15

Example 120

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-
 yl)ethyl)benzamide:



The title compound was prepared analogously to example 81 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 4.6 mg

10

HPLC: (A1) R_t = min

(B1) R_t = min

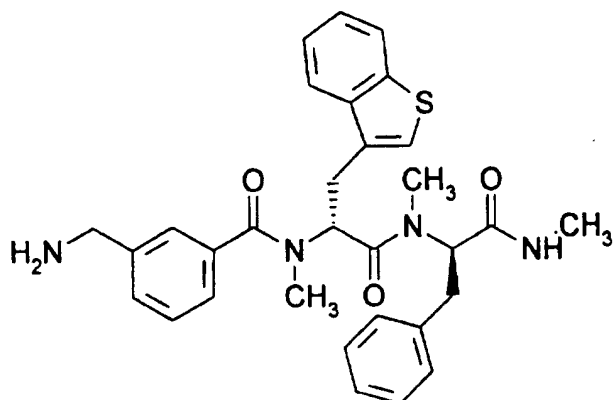
LC-MS: 557.0 (m+1)⁺

15

Example 121

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 82 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 3.1 mg

10

HPLC: (A1) R_t = min

(B1) R_t = min

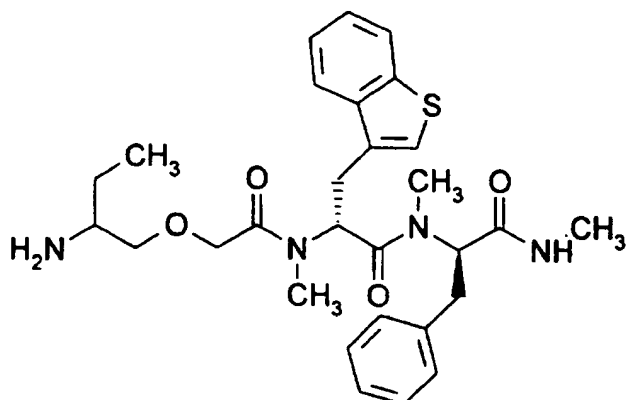
LC-MS: 542.8 (m+1)⁺

15

Example 122

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide:

20



The title compound was prepared analogously to example 83 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 1.2 mg

10

HPLC:(A1) $R_t = 30.48$ min

(B1) $R_t =$ min

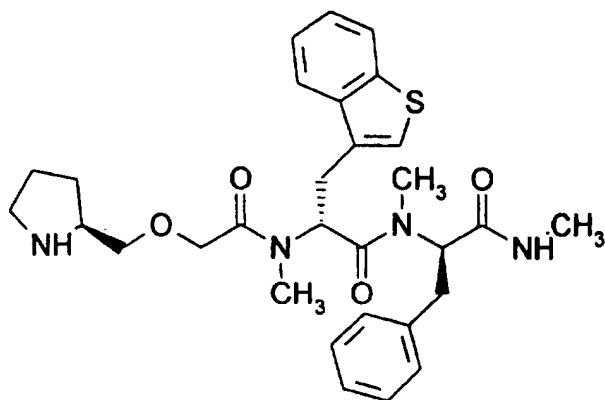
LC-MS: 539.2 (m+1)⁺

15

Example 123

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-

20 yl)propion-amide:



The title compound was prepared analogously to example 84 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 2.9 mg

10

HPLC:(A1) $R_t = 30.47$ min

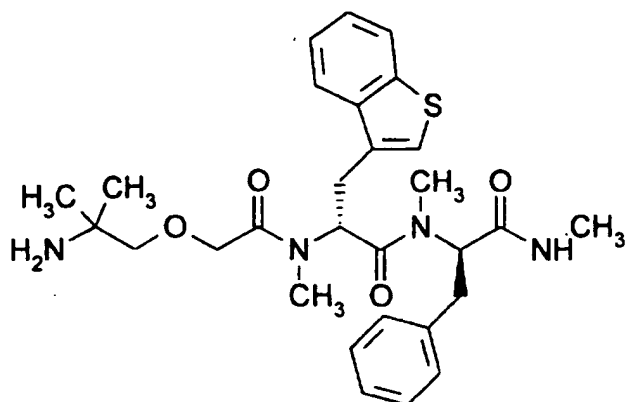
(B1) $R_t =$ min

LC-MS: 550.8 (m+1)⁺

15

Example 124

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-
 20 yl)propionamide:



The title compound was prepared analogously to example 85 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 3.3 mg

10

HPLC: (A1) $R_t = 30.18$ min

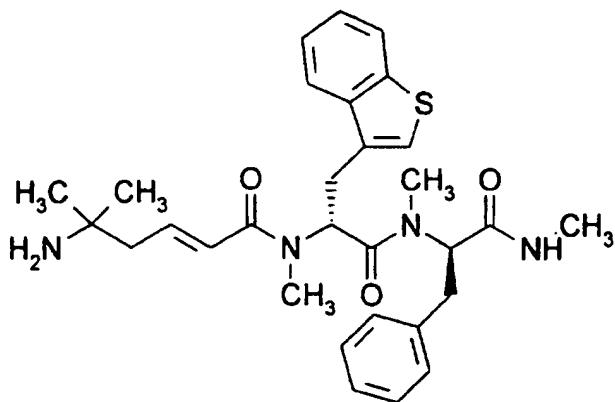
(B1) $R_t = \text{min}$

LC-MS: 539.2 (m+1)⁺

15

Example 125

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-
 yl)ethyl)amide:



The title compound was prepared analogously to example 86 with (2R)-2-(N-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 1.1 mg

10

HPLC: (A1) $R_t = 30.57$ min

(B1) $R_1 = \min$

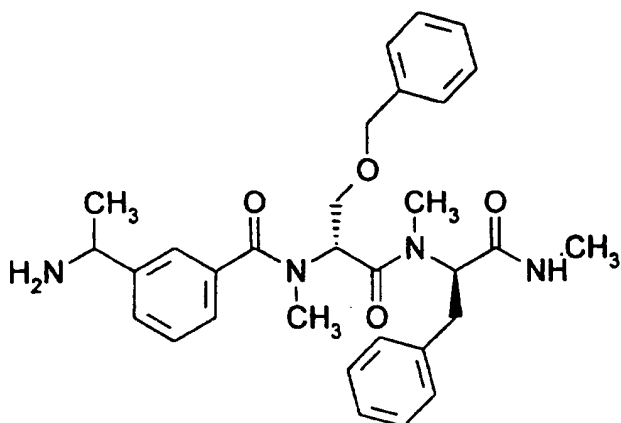
LC-MS: 535.2 (m+1)⁺

15

Example 126

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:

20



The title compound was prepared analogously to example 87 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 15.9 mg

10

HPLC:(A1) $R_t = 30.87$ min

(B1) $R_t = 32.50$ min

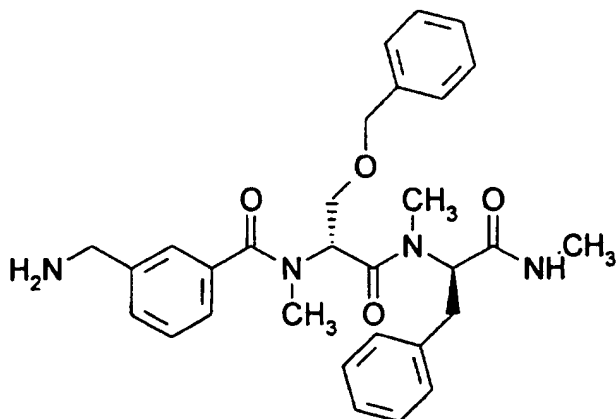
LC-MS: 531.2 (m+1)⁺

15

Example 127

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:

20



The title compound was prepared analogously to example 88 with (2R)-2-(N-
((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
thienyl)propionic acid.

Yield: 13.2 mg

10

HPLC: (A1) $R_t = 30.02$ min

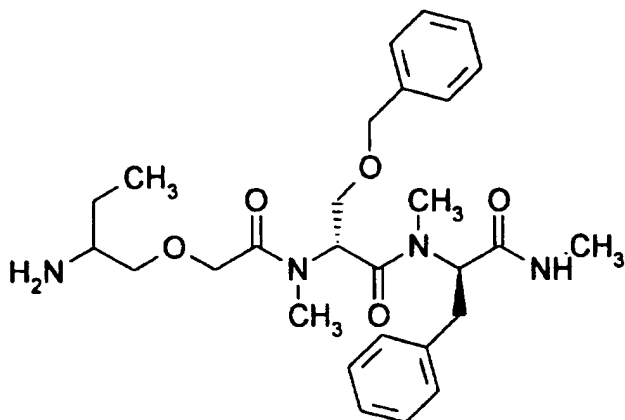
(B1) $R_t = 31.65$ min

LC-MS: 517.0 (m+1)⁺

15

Example 128

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 89 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 14.7 mg

10

HPLC:(A1) R_t = 29.38 min

(B1) R_t = 30.85 min

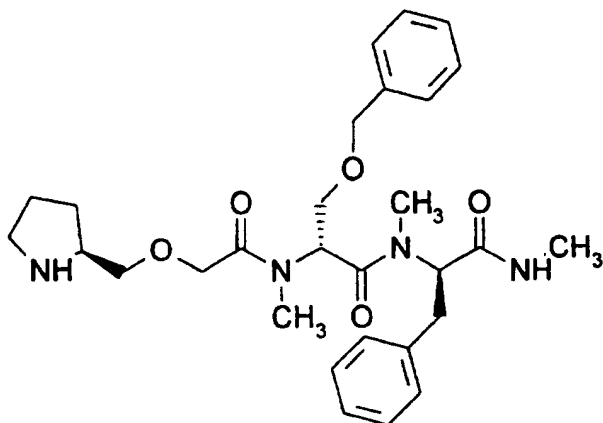
LC-MS: 513.2 (m+1)⁺

15

Example 129

(2R)-2-(N-((((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide:

20



The title compound was prepared analogously to example 90 with (2R)-2-((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-thienyl)propionic acid.

Yield: 17.9 mg

10

HPLC:(A1) $R_t = 29.00$ min

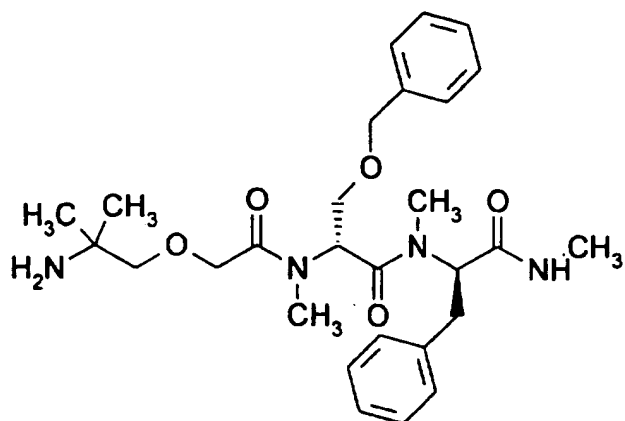
(B1) $R_t = 30.45$ min

LC-MS: 525.0 (m+1)⁺

15

Example 130

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
20 ((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 91 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 16.5 mg

10

HPLC:(A1) R_t = 29.15 min

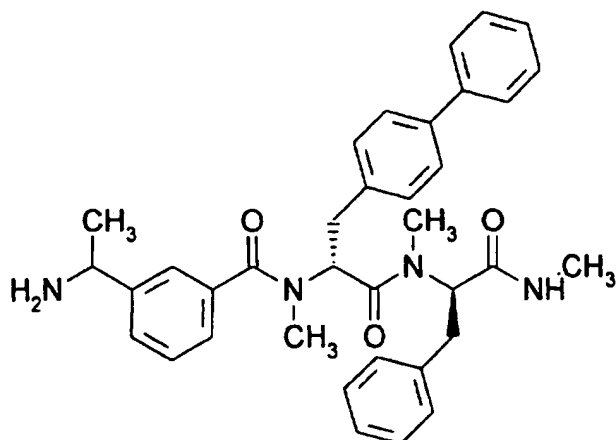
(B1) R_t = 30.57 min

LC-MS: 513.2 (m+1)⁺

15

Example 131

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-
 20 yl)ethyl)benzamide:



The title compound was prepared analogously to example 93 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 7.5 mg

10

HPLC:(A1) $R_t = 34.63$ min

(B1) $R_t =$ min

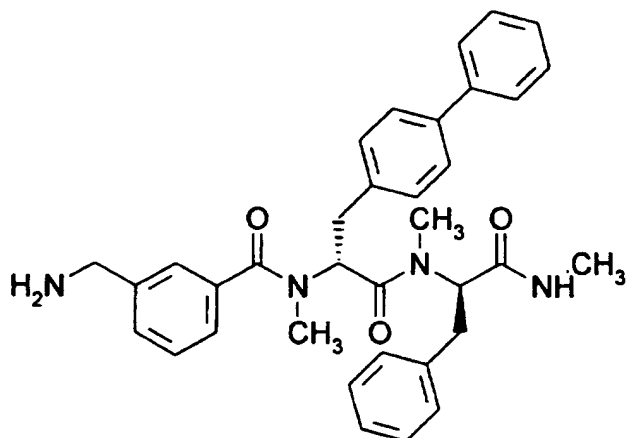
LC-MS: $(m+1)^+$

15

Example 132

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 94 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 9.5 mg

10

HPLC:(A1) R_t = 35.25 min

(B1) R_t = 36.93 min

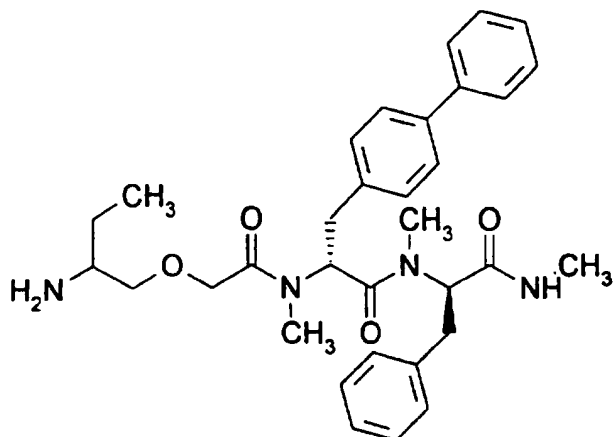
LC-MS: (m+1)⁺

15

Example 133

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 95 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 13.3 mg

10

HPLC:(A1) $R_t = 34.30$ min

(B1) $R_t = 36.10$ min

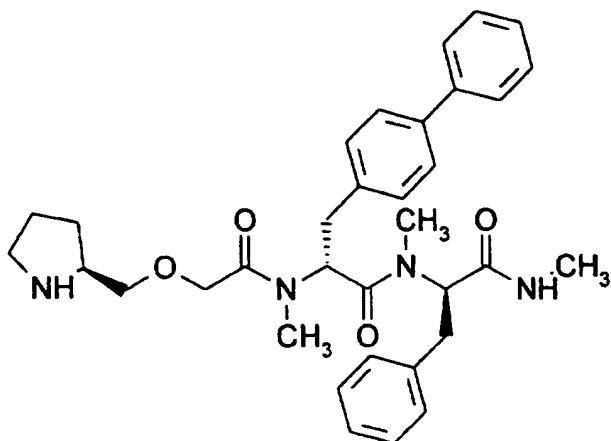
LC-MS: 559.0 (m+1)⁺

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Example 134

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methoxycarbonyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 96 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 20.9 mg

10

HPLC: (A1) $R_t = 34.47$ min

(B1) $R_t = 36.17$ min

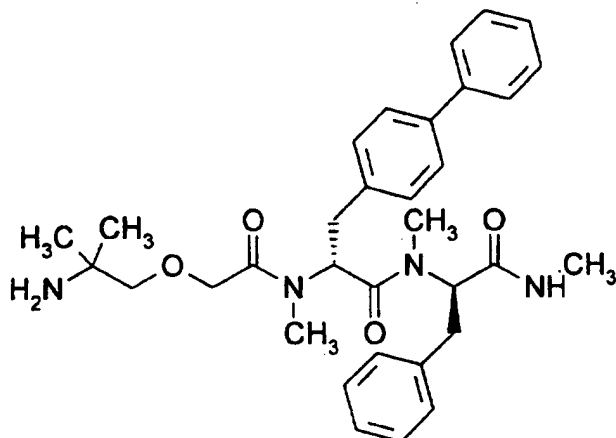
LC-MS: 571.0 ($m+1$)⁺

15

Example 135

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide:

20



The title compound was prepared analogously to example 97 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-phenylpropionic acid
 5 instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-
 thienyl)propionic acid.

Yield: 25.4 mg

10

HPLC:(A1) $R_t = 34.05$ min

(B1) $R_t = 35.78$ min

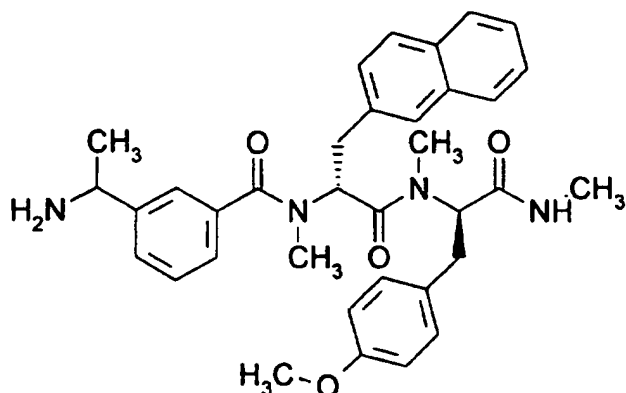
LC-MS: 559.0 (m+1)⁺

15

Example 136

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(2-
 20 naphthyl)ethyl)benzamide:

342



The title compound was prepared analogously to example 76 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 8.3 mg

10

HPLC:(A1) $R_t = 31.32$ min

(B1) $R_t = 32.92$ min

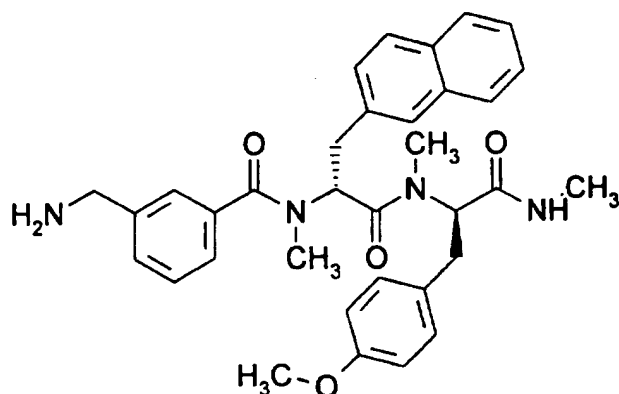
LC-MS: 580.8 (m+1)⁺

15

Example 137

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide:

20



The title compound was prepared analogously to example 77 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 4.1 mg

10

HPLC:(A1) $R_t = 30.62$ min

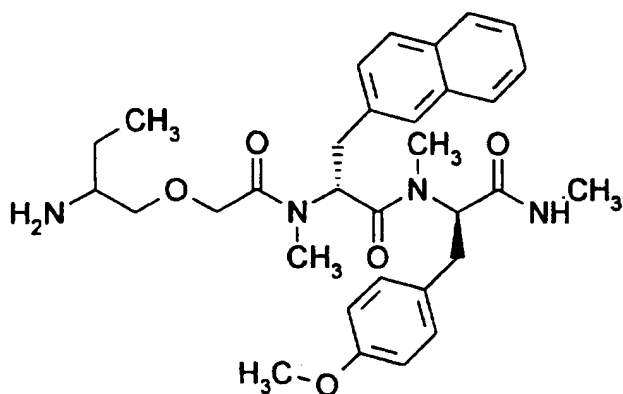
(B1) $R_t =$ min

LC-MS: 566.8 (m+1)⁺

15

Example 138

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide:



The title compound was prepared analogously to example 78 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 18.0 mg

10

HPLC: (A1) $R_t = 30.78$ min

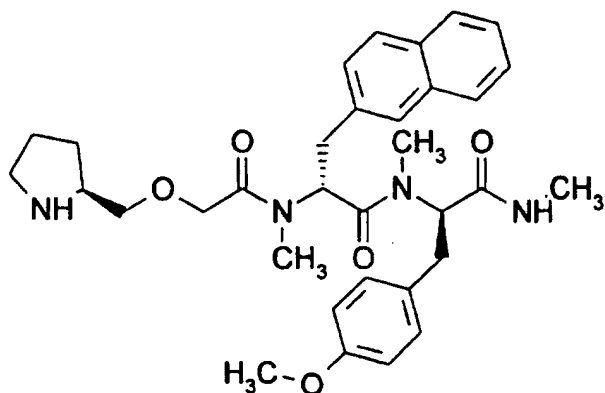
(B1) $R_t = 32.27$ min

LC-MS: 563.2 (m+1)⁺

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Example 139

(2R)-2-(N-(((2S)-2-Pyrrolidiny)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)-
 20 propionamide:



The title compound was prepared analogously to example 79 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 24.0 mg

10

HPLC:(A1) $R_t = 30.85$ min

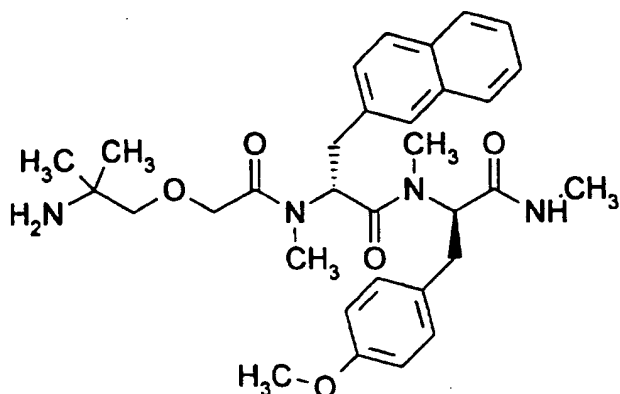
(B1) $R_t = 32.40$ min

LC-MS: 574.8 (m+1)⁺

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Example 140

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propion-
 amide:



The title compound was prepared analogously to example 80 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 15.6 mg

10

HPLC:(A1) $R_t = 30.37$ min

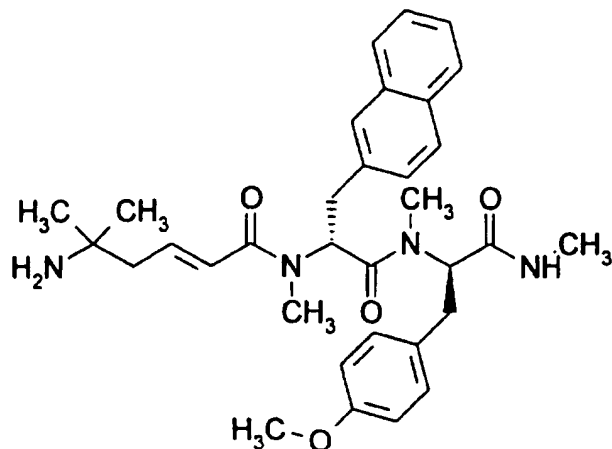
(B1) $R_t = 31.90$ min

LC-MS: 563.2 (m+1)⁺

15

Example 141

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-
 20 naphthyl)-ethyl)amide:



The title compound was prepared analogously to example 140 with (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid instead of (2-(tert-butoxycarbonylamino)-2-methylpropoxy)acetic acid.

Yield: 2.9 mg

HPLC:(A1) R_t = min

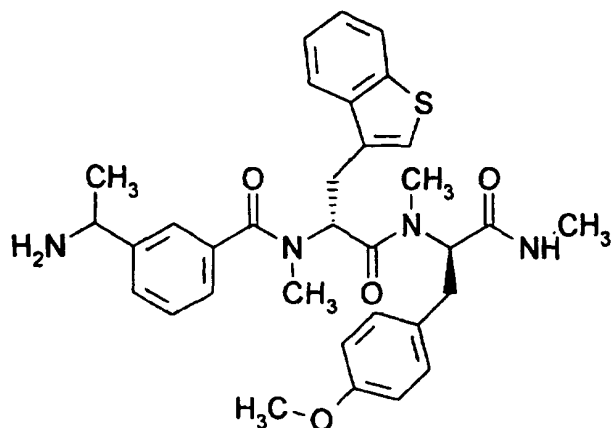
10 (B1) R_t = min

LC-MS: 559.0 (m+1)⁺

Example 142

15

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide:



The title compound was prepared analogously to example 81 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 3.4 mg

10

HPLC:(A1) R_t = 30.90 min

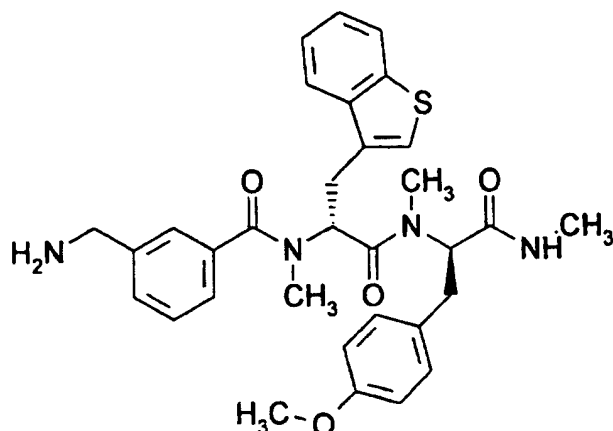
(B1) R_t = min

LC-MS: 586.8 (m+1)⁺

15

Example 143

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-
 20 benzamide:



The title compound was prepared analogously to example 82 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 5.5 mg

10

HPLC:(A1) $R_t = 30.15$ min

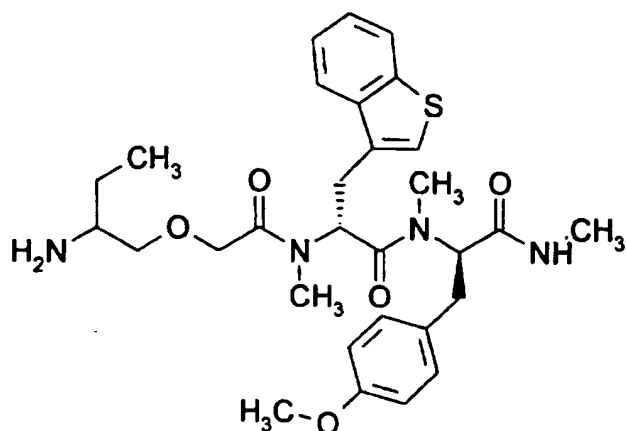
(B1) $R_t =$ min

LC-MS: 573.0 (m+1)⁺

15

Example 144

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-
 yl)propionamide:



The title compound was prepared analogously to example 83 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 7.5 mg

10

HPLC: (A1) $R_t = 30.18$ min

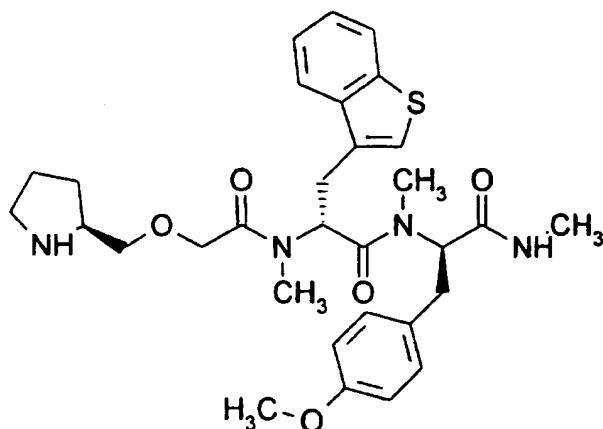
(B1) $R_t =$ min

LC-MS: 569.0 (m+1)⁺

15

Example 145

(2R)-2-(N-(((2S)-2-Pyrrolidiny)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-
 20 (benzo[b]thiophen-3-yl)propionamide:



The title compound was prepared analogously to example 84 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 10.5 mg

10

HPLC:(A1) $R_t = 30.20$ min

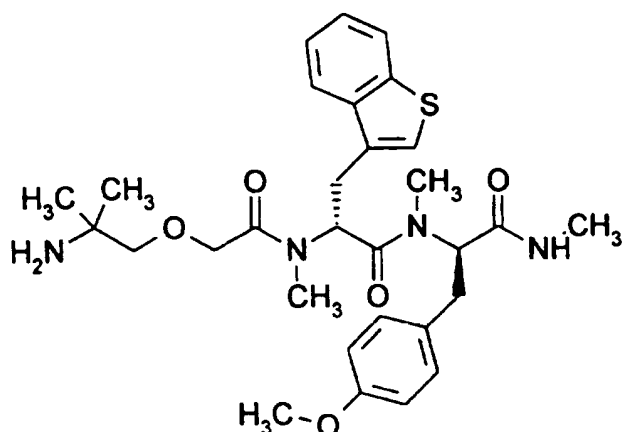
(B1) $R_t = \text{min}$

LC-MS: 581.0 (m+1)⁺

15

Example 146

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-
 3-yl)propionamide:



The title compound was prepared analogously to example 85 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 9.9 mg

10

HPLC: (A1) $R_t = 29.87$ min

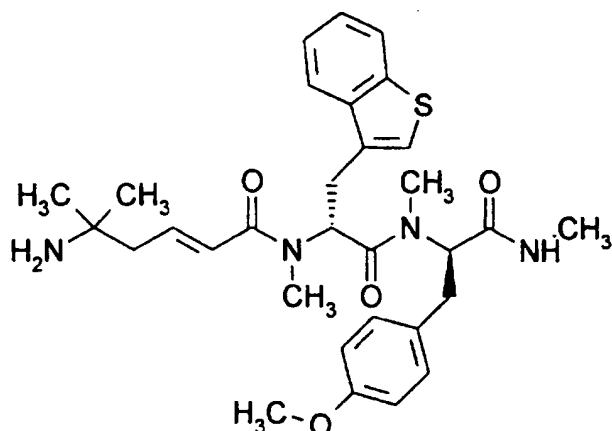
(B1) $R_t =$ min

LC-MS: 569.0 (m+1)⁺

15

Example 147

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-
 20 (benzo[b]thiophen-3-yl)ethyl)amide:



The title compound was prepared analogously to example 86 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 4.0 mg

10

HPLC:(A1) $R_t = 30.42$ min

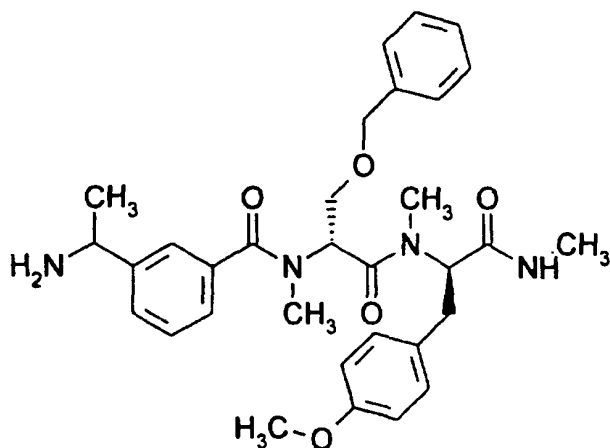
(B1) $R_t =$ min

LC-MS: $(m+1)^+$

15

Example 148

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-
 20 (benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 87 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 6.1 mg

10

HPLC:(A1) $R_t = 30.82$ min

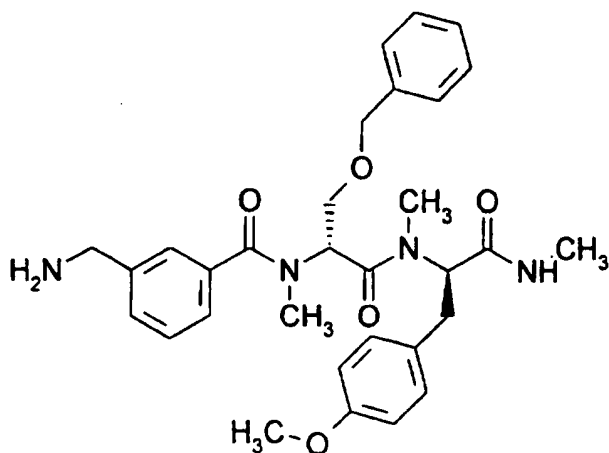
(B1) $R_t =$ min

LC-MS: 561.2 (m+1)⁺

15

Example 149

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 20 2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide:



The title compound was prepared analogously to example 88 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 7.3 mg

10

HPLC:(A1) $R_t = 36.23$ min

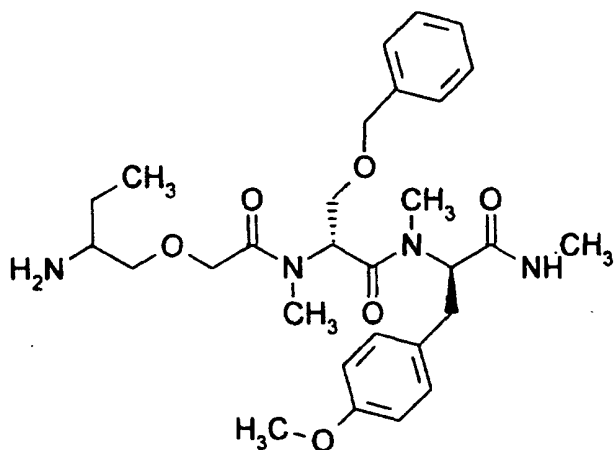
(B1) $R_t = \text{min}$

LC-MS: 547.0 (m+1)⁺

15

Example 150

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide:



The title compound was prepared analogously to example 89 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 2.4 mg

10

HPLC:(A1) R_t = min

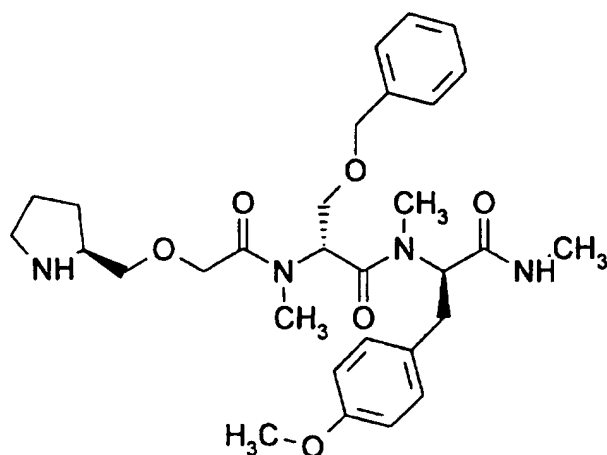
(B1) R_t = min

LC-MS: $(m+1)^+$

15

Example 151

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
 20 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-
 (benzyloxy)propionamide:



The title compound was prepared analogously to example 90 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 19.0 mg

10

HPLC: (A1) $R_t = 28.65$ min

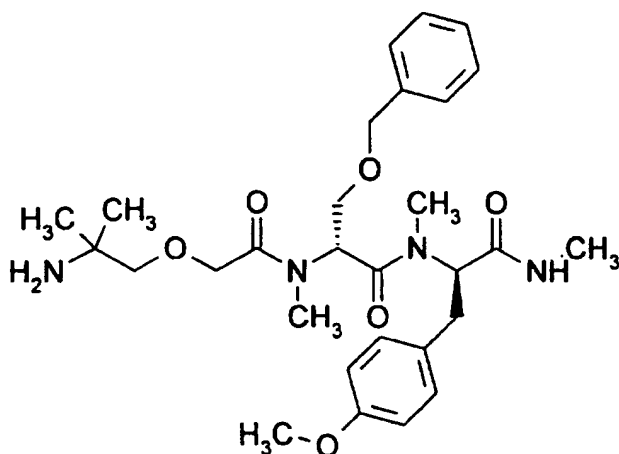
(B1) $R_t = 30.02$ min

LC-MS: 555.0 ($m+1$)⁺

15

Example 152

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
 20 ((1R)-1-(methoxycarbonyl)-2-(4-methoxyphenyl)ethyl)-3-
 (benzyloxy)propionamide:



The title compound was prepared analogously to example 91 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 20.5 mg

10

HPLC:(A1) $R_t = 28.80$ min

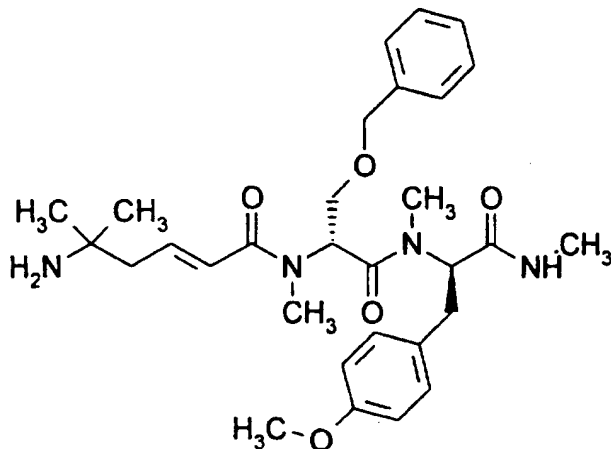
(B1) $R_t = 30.17$ min

LC-MS: 543.2 (m+1)⁺

15

Example 153

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
 20 ((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-
 (benzyloxy)ethyl)amide:



The title compound was prepared analogously to example 92 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 4.0 mg

10

HPLC:(A1) $R_t = 28.37$ min

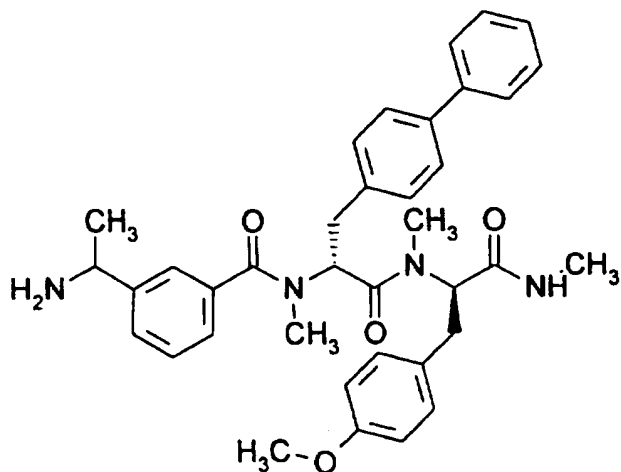
(B1) $R_t =$ min

LC-MS: 539.2 (m+1)⁺

15

Example 154

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
 20 (methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(biphen-4-
 yl)ethyl)benzamide:



The title compound was prepared analogously to example 93 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 8.2 mg

10

HPLC:(A1) R_t = min

(B1) R_t = min

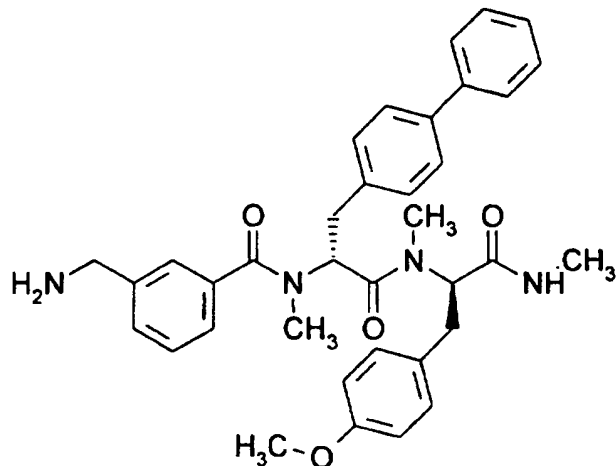
LC-MS: 607.0 (m+1)⁺

15

Example 155

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
 2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide:

20



The title compound was prepared analogously to example 94 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 7.2 mg

10

HPLC:(A1) R_t = min

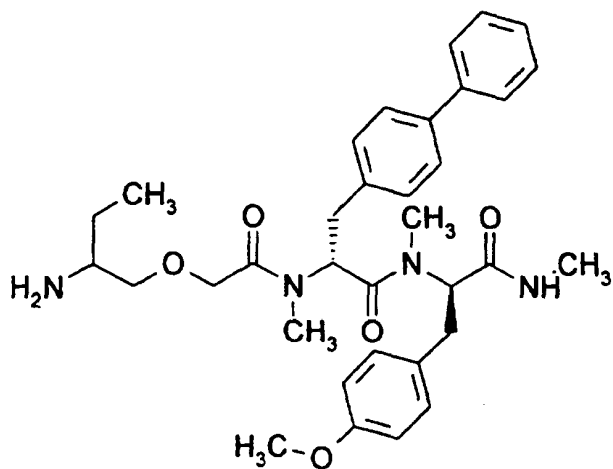
(B1) R_t = min

LC-MS: 593.2 (m+1)⁺

15

Example 156

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-
 20 yl)propionamide:



The title compound was prepared analogously to example 95 with (2R)-2-(N-
 ((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
 5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
 methylamino)-3-(2-thienyl)-propionic acid.

Yield: 6.0 mg

10

HPLC:(A1) R_t = min

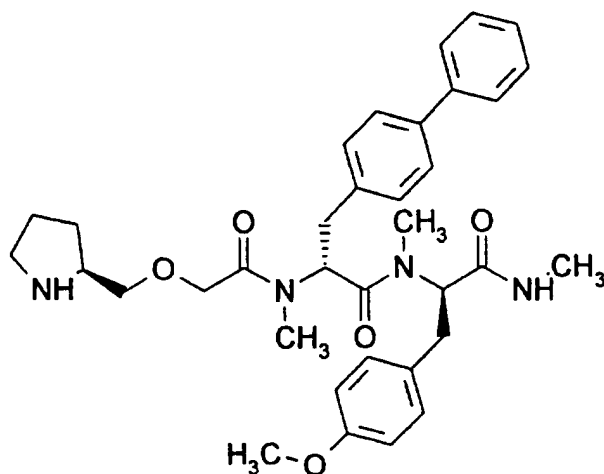
(B1) R_t = min

LC-MS: 589.2 (m+1)⁺

15

Example 157

(2R)-2-(N-(((2S)-2-Pyrrolidiny)methoxy)acetyl)-N-methylamino)-N-methyl-
 N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-
 20 yl)propionamide:



The title compound was prepared analogously to example 96 with (2R)-2-(N-
((9H-fluoren-9-yl)methoxy-carbonyl)-N-methylamino)-3-(4-methoxyphenyl)-
5 propionic acid instead of (2R)-2-(N-(9H-fluoren-9-ylmethoxycarbonyl)-N-
methylamino)-3-(2-thienyl)-propionic acid.

Yield: 10.0 mg

10

HPLC:(A1) R_t = min

(B1) R_t = min

LC-MS: 601.0 (m+1)⁺

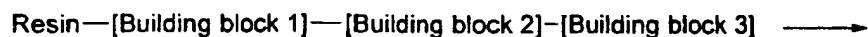
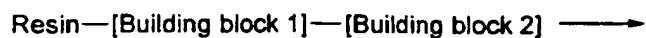
15

General Procedure for Example 158-533

The following 376 compounds were prepared as single entities by parallel
20 synthesis on a solid support using an Fmoc strategy on an Advanced ChemTech
Model 384 HTS employing HATU/HOAt (O-(7-azabenzotriazol-1-yl)-1,1,3,3-
tetramethyluronium hexafluorophosphate/1-hydroxy-7-azabenzotriazole)
mediated amidecoupling in dimethylformamide (DMF) according to a protocol

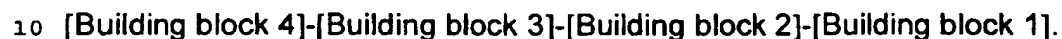
known for those skilled in the art.

The compounds were prepared sequentially according to the following equation



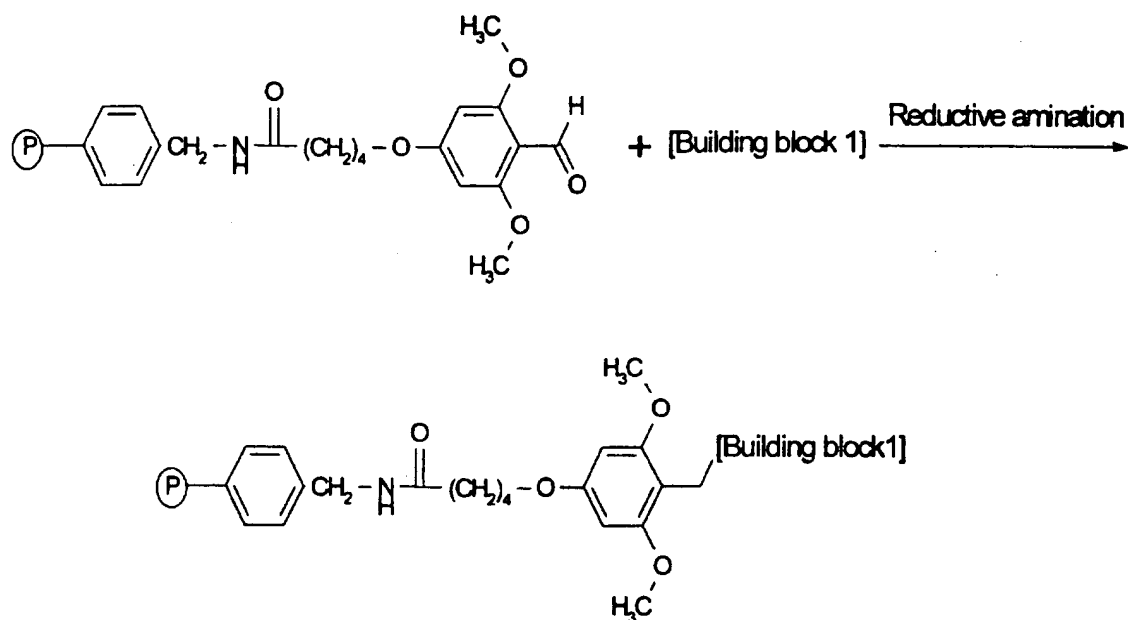
5

and were simultaneously deprotected and cleaved from the resin with 50% trifluoroacetic acid (TFA) in dichloromethane (DCM) to give the desired compounds as individual entities according to the following formula



The starting resins were all prepared separately by reductive amination of [Building block 1] and a 5-(4-formyl-3,5-dimethoxyphenoxy)valerate resin as described in Example 44 for N-Me-PAL.

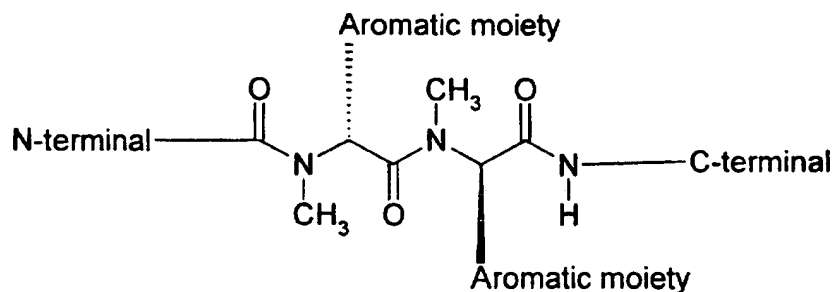
15



The substitution capacities of the resins were 0.5 - 0.7 mmol/g determined by UV monitoring of the deprotection of the Fmoc protection group.

5

All 376 compounds are based on a scaffold and four varying groups according to the following formula, which is included in general formula I:



10

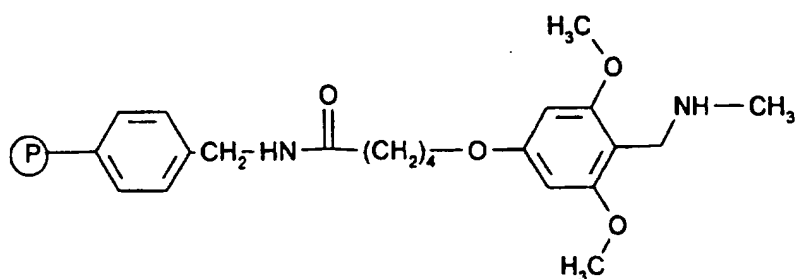
The 376 compounds were prepared as three separate libraries based on total combination of four selected building blocks (see example 158-253, example 254-353 and example 354-533) and prepared analogously to the procedure described in Example 158.

15

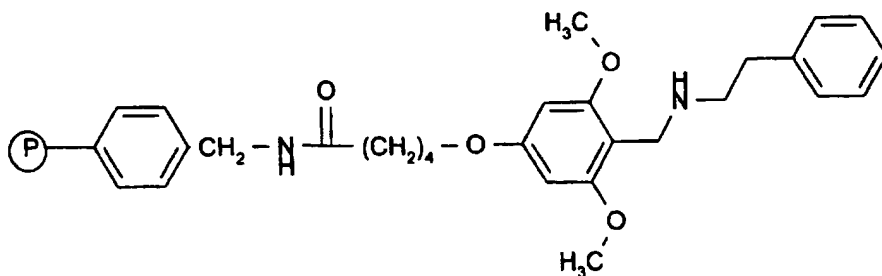
The following resins, here depicted as Resin-[Building block 1] were used:

Resins

5 Name: N-Me-PAL (described in Example 44)

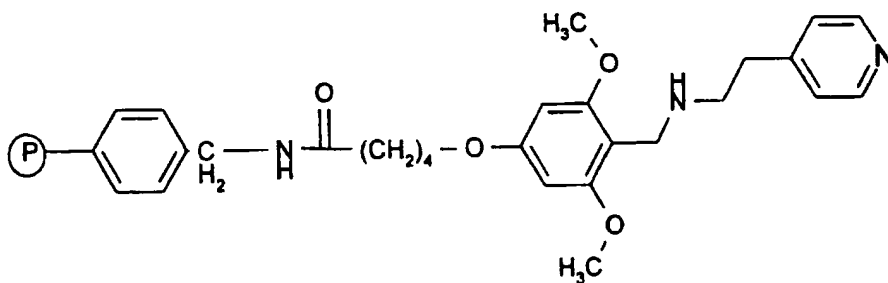


Name: N-Phenethyl-PAL (prepared analogously to N-Me-PAL)



10

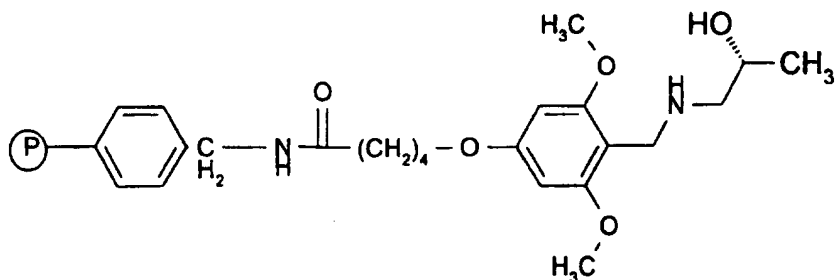
Name: N-(4-Pyridyl)ethyl-PAL (prepared analogously to N-Me-PAL)



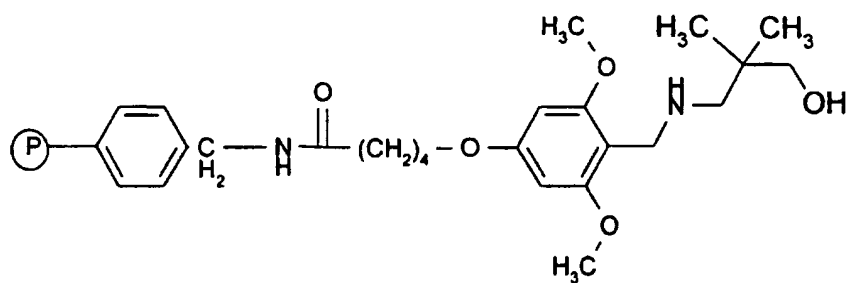
15

Name: N-((S)-2-Hydroxypropyl)-PAL (prepared analogously to N-Me-PAL)

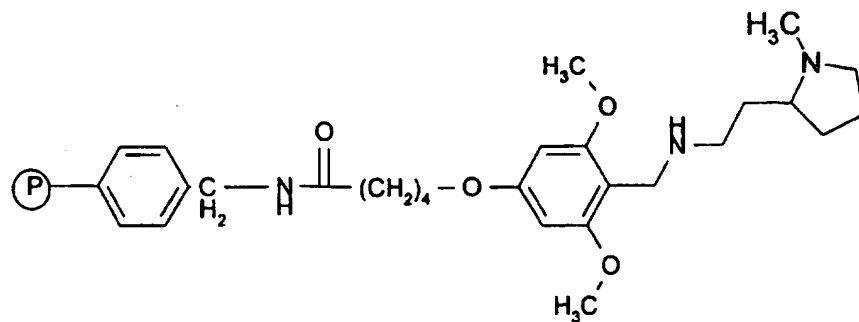
367



Name: N-(2,2-Dimethyl-3-hydroxypropyl)-PAL (prepared analogously to N-Me-
5 PAL)



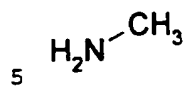
Name: N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL (prepared analogously to N-Me-
10 PAL)



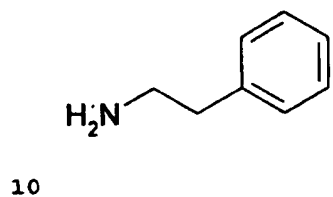
15 The following building blocks were used:

Building block 1

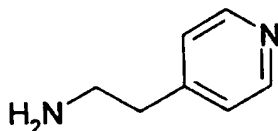
Name: Methylamine



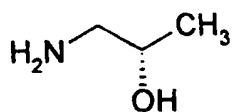
Name: Phenethylamine



Name: 2-(4-pyridyl)ethylamine

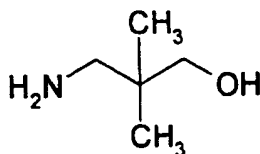


15 Name: (S)-2-Hydroxypropylamine

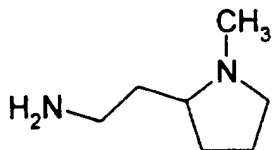


Name: 2,2-Dimethyl-3-hydroxypropylamine

20



Name: 2-(1-Methylpyrrolidine-2-yl)ethylamine

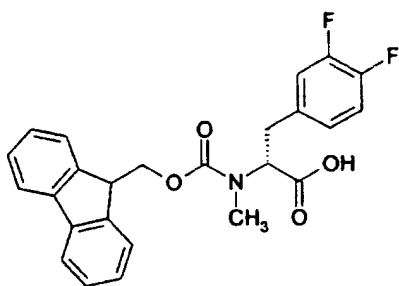


5

Building block 2

Name: (2R)-2-[N-(9H-Fluoren-9-yl)methoxycarbonyl]-N-methylamino]-3-(3,4-difluorophenyl)propionic acid

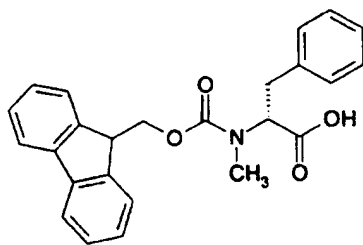
10 Abbreviation: Fmoc-N-Me-D-Phe(3,4-F,F)-OH



Name: (2R)-2-(N-(((9H-Flouren-9-yl)methoxy)carbonyl)-N-methylamino)-3-

15 phenylpropionic acid

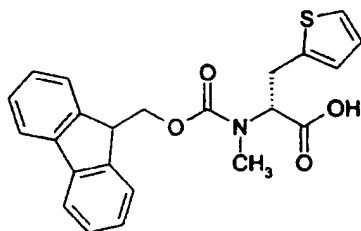
Abbreviation: Fmoc-N-Me-D-Phe-OH



Name: (2R)-2-(N-(9H-Fluoren-9-ylmethoxycarbonyl)-N-methylamino)-3-(2-

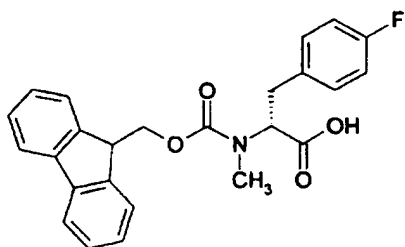
20 thienyl)propionic acid

Abbreviation: Fmoc-N-Me-D-ThiAla-OH



- 5 Name: (2R)-2-[N-(9H-Fluoren-9-yl)methoxycarbonyl]-N-methylamino]-3-(4-fluorophenyl)propionic acid

Abbreviation: Fmoc-N-Me-D-Phe(4-F)-OH

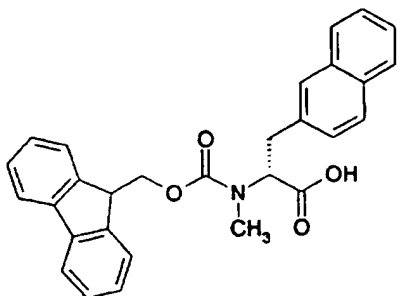


10

Building block 3

- 15 Name: (2R)-2-(N-(((9H-Flouren-9-yl)methoxy)carbonyl)-N-methylamino)-3-(2-naphthyl)propionic acid

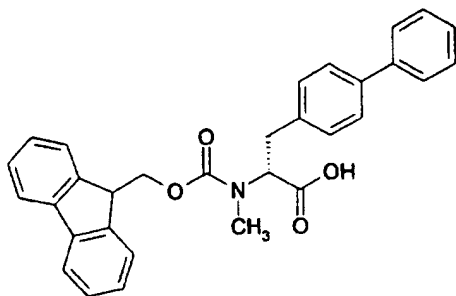
Abbreviation: Fmoc-N-Me-D-2-Nal-OH



Name: (2R)-3-(Biphenyl-4-yl)-2-(N-((9H-fluoren-9-yl)methoxycarbonyl)-N-methylamino)propionic acid

Abbreviation: Fmoc-N-Me-D-Phe(4-Phe)-OH

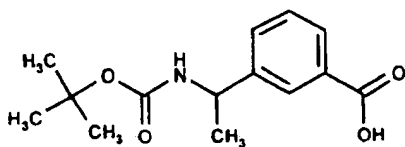
5



10 Building block 4

Name: 3-(1-(tert-Butyloxycarbonylamino)ethyl)benzoic acid

Abbreviation: Boc-AEB-OH

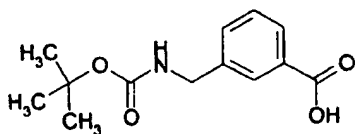


15

Name: 3-(t-Butyloxycarbonylaminomethyl)benzoic acid

Abbreviation: Boc-AMB-OH

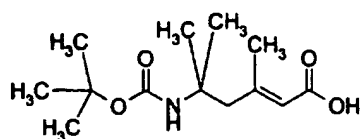
20



Name: (2E)-5-tert-Butoxycarbonylamino-3,5-dimethylhex-2-enoic acid

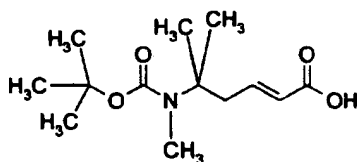
Abbreviation: Boc-ADH-OH

5



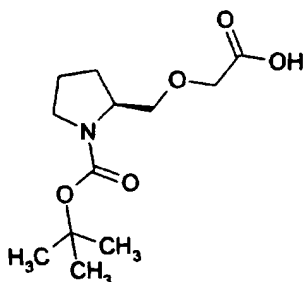
10 Name: (2E)-5-(N-(tert-Butoxycarbonyl)-N-methylamino)-5-methylhex-2-enoic acid.

Abbreviation: Boc-MAMH-OH



15 Name: (2S)-2-(((Carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butyl ester

Abbreviation: Boc-SPMA-OH

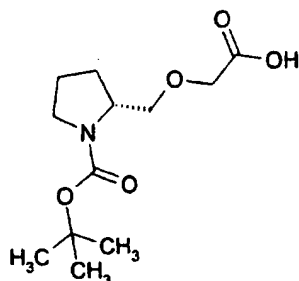


20

Name: (2R)-2-(((Carboxy)methoxy)methyl)pyrrolidin-1-carboxylic acid tert-butyl

ester

Abbreviation: Boc-RPMA-OH

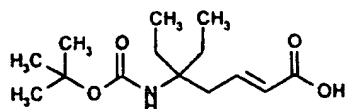


5

Name: (2E) 5-tert-Butoxycarbonylamino-5-ethylhept-2-enoic acid

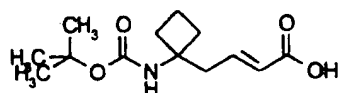
Abbreviation: Boc-AEHA-OH

10



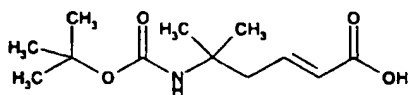
Name: (2E)-4-(1-(tert-Butoxycarbonylamino)cyclobutyl)but-2-enoic acid

15 Abbreviation: Boc-ACBB-OH



20 Name: (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid

Abbreviation: Boc-AMH-OH



Example 158

5

The N-Me-PAL resin ([building block 1] attached to resin) (0.05 mmol) with a substitution capacity of 0.6 mmol/g was repeatedly (4 times) swelled in dichloromethane and dimethylformamide for 2 min and filtered.

1.0 Coupling: DIEA (0.025 mmol) in DCM (0.034 ml), HATU (0.0125 mmol) in DMF (0.5 ml), a solution of HOAt (0.0125 mmol) and Fmoc-N-Me-D-Phe(4-F)-OH [building block 2] (0.0125 mmol) in DMF (0.5 ml) and DMF (0.5 ml) were added. The mixture was allowed to shake for 16 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

1.5 Coupling: DIEA (0.00625 mmol) in DCM (0.0085 ml), HATU (0.003125 mmol) in DMF (0.125 ml), a solution of HOAt (0.003125 mmol) and Fmoc-N-Me-D-Phe(4-F)-OH [building block 2] (0.003125 mmol) in DMF (1.25 ml) were added. The mixture was allowed to shake for 4 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

Deprotection: A solution of 20% piperidine in DMF (1.5 ml) was added and the mixture was shaken for 20 min. The resin was repeatedly (7 times) swelled in dimethylformamide for 90 sec and filtered.

2.0 Coupling: DIEA (0.025 mmol) in DCM (0.034 ml), HATU (0.0125 mmol) in DMF (0.5 ml), a solution of HOAt (0.0125 mmol) and Fmoc-N-Me-D-2-Nal-OH [building block 3] (0.0125 mmol) in DMF (0.5 ml) and DMF (0.5 ml) were added. The mixture was allowed to shake for 16 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

2.5 Coupling: DIEA (0.00625 mmol) in DCM (0.0085 ml), HATU (0.003125 mmol) in DMF (0.125 ml), a solution of HOAt (0.003125 mmol) Fmoc-N-Me-D-2-Nal-OH [building block 3] (0.003125 mmol) in DMF (1.25 ml) were added. The mixture

was allowed to shake for 4 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filter d.

Deprotection: A solution of 20% piperidine in DMF (1.5 ml) was added and the mixture was shaken for 20 min. The resin was repeatedly (7 times) swelled in
5 dimethylformamide for 90 sec and filtered.

3.0 Coupling: DIEA (0.025 mmol) in DCM (0.034 ml), HATU (0.0125 mmol) in DMF (0.5 ml), a solution of HOAt (0.0125 mmol) and Boc-AMH-OH [building block
10 4] (0.0125 mmol) in DMF (0.5 ml) and DMF (0.5 ml) were added. The mixture was allowed to shake for 16 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

3.5 Coupling: DIEA (0.00625 mmol) in DCM (0.0085 ml), HATU (0.003125 mmol) in DMF (0.125 ml), a solution of HOAt (0.003125 mmol) and Boc-AMH-OH [building
15 block 4] (0.003125 mmol) in DMF (1.25 ml) were added. The mixture was allowed to shake for 4 hours. The resin was repeatedly (5 times) swelled in dimethylformamide for 90 sec and filtered.

The resin was repeatedly (3 times) swelled in dichloromethane for 90 sec and filtered.

20

The compound was cleaved off the resin and deprotected by shaking for 10 min at -5 °C with a 50% solution of trifluoroacetic acid in dichloromethane (1.5 ml).
25 Ethanol (1.5 ml) was added and the mixture was filtered and concentrated in vacuo to give the desired compound.

The final product obtained was characterized by analytical RP-HPLC (retention time) and by LC-MS (molecular mass).

30

The RP-HPLC analysis was performed on a Waters HPLC system consisting of

Waters™ 600S Controller, Waters™ 996 Photodiode Array Detector, Waters™ 717 Autosampler, Waters™ 616 Pump, Waters™ 3 mm x 150 mm 3.5m C-18 Symmetry and Millennium QuickSet Control Ver. 2.15 using UV detection at 214 nm. A gradient of 5% to 90% acetonitrile/0.1 % trifluoroacetic acid/ water during
5 15 min at 1 ml/min.

The LC-MS analysis was performed on a PE Sciex API 100 LC/MS System using a Waters™ 3 mm x 150 mm 3.5m C-18 Symmetry column and positive ionspray with a flow rate at 20 ml/min.

10

15 EXAMPLES 159-253

The following 95 compounds were synthesized in parallel as individual entities analogously to example 158 on an Advanced ChemTech Model 384 HTS using
20 the following ChemFile to control the operation of the synthesizer (Advanced ChemTech Operator's Manual, version 1.2 July 1996, pp. 4-13):

ChemFile C:\ACT\CHEMFILE\2PETER.CHM Page 1

25

- 1 Flush Arm1 with DMF and NMP, Arm2 with DCM and DMF4
- 2 Empty RB1_1to96 for 3.000 minute(s)
- 3
- 30 4 Dispense System Fluid Dualarms_1+4* 1000µl to RB1_1to96[1-96]
- 5 Mix "RB1_1to96" for 2.00 minutes at 700 rpm(s)

- 6 Wait for 28.000 minute(s)
- 7 Empty RB1_1to96 for 3.000 minute(s)
- 8
- 9 REM Syntesestart her. Aminosyre 1
- 5 10 Dispense Sequence C:\ACT\displist\A1.DSP with 500 μ l to RB1_1to96 rack using DMF
- 11 Dispense Sequence C:\ACT\displist\A2.DSP with 500 μ l to RB1_1to96 rack using DMF
- 12 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 10 13 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- 14 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 15 Dispense System Fluid Dualarms_1+4* 500 μ l to RB1_1to96 [1-96]
- 16 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
- 15 17 Wait for 25.000 minute(s)
- 18 Repeat from step 16, 31 times
- 19 Pause
- 20 Empty RB1 1to96 for 3.000 minute(s)
- 21 Goto ChemFile WASH_DMF.CHM, line 1
- 20 22
- 23 REM Anden kobling 1ste AA
- 24 Dispense Sequence C:\ACT\displist\A1.DSP with 125 μ l to RB1_1to96 rack using DMF
- 25 Dispense Sequence C:\ACT\displist\A2.DSP with 125 μ l to RB1_1to96 rack
- 25 using DMF
- 26 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 27 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- 28 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 30 29 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB1_1to96 [1-96]
- 30 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)

- 31 Wait for 25.000 minute(s)
32 Repeat from step 30, 9 times
33 Empty RB1_1to96 for 3.000 minute(s)
34 Pause
5 35 Goto ChemFile COUPLING.CHM, line 1
36 Pause
37
38 Goto ChemFile WASH_DMF.CHM, line 1
39 Goto ChemFile DEPROTEC.CHM, line 1
10 40 Goto ChemFile WASH_DMF.CHM, line 1
41
42 REM Her starter anden aminosyre-kobling
43 Dispense Sequence C:\ACT\displist\B1.DSP with 500µl to RB1_1to96 rack
using DMF
15 44 Dispense Sequence C:\ACT\displist\B2.DSP with 500µl to RB1_1to96 rack
using DMF
45 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
46 Transfer 500µl from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
47 Transfer 68µl from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using
20 DMF
48 Dispense System Fluid Dualarms_1+4* 500µl to RB1_1to96 [1-96]
49 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
50 Wait for 25.000 minute(s)
51 Repeat from step 49, 31 times
25 52
53 Empty RB1 1to96 for 3.000 minute(s)
54 Goto ChemFile WASH_DMF.CHM, line 1
55
56 REM Anden AA. Anden kobling
30 57 Dispense Sequence C:\ACT\displist\B1.DSP with 125µl to RB1_1to96 rack
using DMF

58 Dispense Sequence C:\ACT\displst\B2.DSP with 125 μ l to RB1_1to96 rack
using DMF

59 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)

60 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF

5 61 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using
DMF

62 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB1_1to96 [1-96]

63 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)

64 Wait for 25.000 minute(s)

10 65 Repeat from step 63, 9 times

66 Empty RB1 1to96 for 3.000 minute(s)

67 Goto ChemFile WASH_DMF.CHM, line 1

68 Goto ChemFile DEPROTEC.CHM, line 1

69 Goto ChemFile WASH_DMF.CHM, line 1

15 70

71 Pause

72

73 REM N-terminalkobling starter her

74 Dispense Sequence C:\ACT\displst\N1N2N3N4.DSP with 500 μ l to RB1_1to96
20 rack using DMF

75 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)

76 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF

77 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF

78 Dispense System Fluid Dualarms_1+4* 500 μ l to RB1_1to96 [1-96]

25 79 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)

80 Wait for 25.000 minute(s)

81 Repeat from step 79, 20 times

82 Empty RB1 1to96 for 3.000 minute(s)

83 Goto ChemFile WASH_DMF.CHM, line 1

30 84

85 REM N-terminal. Anden kobling

- 86 Dispense Sequence C:\ACT\displist\N1N2N3N4.DSP with 125µl to RB1_1to96 rack using DMF
- 87 Mix "RB1_1to96" for 1.00 minutes at 600 rpm(s)
- 88 Transfer 125µl from REAGENT_3[1] (HATU) to RB1_1to96 [1-96] using DMF
- 5 89 Transfer 20µl from Monomer1to36 [10] (DIEA) to RB1_1to96 [1-96] using DMF
- 90 Dispense System Fluid Dualarms_1+4* 1250µl to RB1_1to96 [1-96]
- 91 Mix "RB1_1to96" for 5.00 minutes at 750 rpm(s)
- 92 Wait for 25.000 minute(s)
- 93 Repeat from step 91, 9 times
- 10 94 Empty RB1 1to96 for 3.000 minute(s)
- 95 Goto ChemFile WASH_DMF.CHM, line 1
- 96 Goto ChemFile DEPROTEC.CHM, line 1
- 97 Goto ChemFile WASH_DMF.CHM, line 1
- 98

15

-
- 20 The building blocks were selected from the following groups:

[Building block 1]: N-Me-PAL, N-Phenethyl-PAL, N-(4-Pyridyl)ethyl-PAL, N-((S)-2-Hydroxypropyl)-PAL, N-(2,2-Dimethyl-3-hydroxypropyl)-PAL and N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL.

25

[Building block 2]: Fmoc-N-Me-D-Phe(4-F)-OH and Fmoc-N-Me-D-Phe(3,4-F,F)-OH.

[Building block 3]: Fmoc-N-Me-D-Nal-OH and Fmoc-N-Me-D-Phe(4-Phe)-OH.

30

[Building block 4]: Boc-AMH-OH, Boc-ACBB-OH, Boc-SPMA-OH and Boc-AEB-OH.

See Table 1

5

EXAMPLES 254-353

- 10 The following 100 compounds were synthesized in parallel as individual entities analogously to example 158 on an Advanced ChemTech Model 384 HTS using the following ChemFiles to control the operation of the synthesizer (Advanced ChemTech Operator's Manual, version 1.2 July 1996, pp. 4-13):

15

ChemFile C:\ACT\CHEMFILE\3PETER.CHM Page 1

- 20 1 Flush Arm1 with DMF and NMP, Arm2 with DCM and DMF4
2 Empty RB2_1to96 for 3.000 minute(s)
3
4 Dispense System Fluid Dualarms_1+4* 1000µl to RB2_1to96[1-96]
5 Mix "RB2_1to96" for 2.00 minutes at 700 rpm(s)
25 6 Wait for 28.000 minute(s)
7 Empty RB2_1to96 for 3.000 minute(s)
8
9 REM Syntesestart her. Aminosyre 1
10 Dispense Sequence C:\ACT\displist\A1.DSP with 500µl to RB2_1to96 rack
30 using DMF
11 Dispense Sequence C:\ACT\displist\A2.DSP with 500µl to RB2_1to96 rack
using DMF

- 12 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
- 13 Transfer 500 μ l from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
- 14 Transfer 68 μ l from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
- 5 15 Dispense System Fluid Dualarms_1+4* 500 μ l to RB2_1to96 [1-96]
- 16 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
- 17 Wait for 25.000 minute(s)
- 18 Repeat from step 16, 31 times
- 19 Pause
- 10 20 Empty RB2_1to96 for 3.000 minute(s)
- 21 Goto ChemFile WASH_DMF.CHM, line 1
- 22
- 23 REM Anden kobling 1ste AA
- 24 Dispense Sequence C:\ACT\displist\A1.DSP with 125 μ l to RB2_1to96 rack
- 15 using DMF
- 25 Dispense Sequence C:\ACT\displist\A2.DSP with 125 μ l to RB2_1to96 rack using DMF
- 26 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
- 27 Transfer 125 μ l from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
- 20 28 Transfer 20 μ l from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
- 29 Dispense System Fluid Dualarms_1+4* 1250 μ l to RB2_1to96 [1-96]
- 30 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
- 31 Wait for 25.000 minute(s)
- 25 32 Repeat from step 30, 7 times
- 33 Empty RB2_1to96 for 3.000 minute(s)
- 34 Goto ChemFile WASH_DMF.CHM, line 1
- 35 Pause
- 36
- 30 37 Goto ChemFile DEPROTEC.CHM, line 1
- 38 Goto ChemFile WASH_DMF.CHM, line 1

- 39
- 40 REM Her starter anden aminosyre-kobling
- 41 Dispense Sequence C:\ACT\displist\B1.DSP with 500µl to RB2_1to96 rack using DMF
- 5 42 Dispense Sequence C:\ACT\displist\B2.DSP with 500µl to RB2_1to96 rack using DMF
- 43 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
- 44 Transfer 500µl from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
- 45 Transfer 68µl from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using
- 10 DMF
- 46 Dispense System Fluid Dualarms_1+4* 500µl to RB2_1to96 [1-96]
- 47 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
- 48 Wait for 25.000 minute(s)
- 49 Repeat from step 47, 31 times
- 15 50
- 51 Empty RB2_1to96 for 3.000 minute(s)
- 52 Goto ChemFile WASH_DMF.CHM, line 1
- 53
- 54 REM Anden AA. Anden kobling
- 20 55 Dispense Sequence C:\ACT\displist\B1.DSP with 125µl to RB2_1to96 rack using DMF
- 56 Dispense Sequence C:\ACT\displist\B2.DSP with 125µl to RB2_1to96 rack using DMF
- 57 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
- 25 58 Transfer 125µl from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
- 59 Transfer 20µl from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
- 60 Dispense System Fluid Dualarms_1+4* 1250µl to RB2_1to96 [1-96]
- 61 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
- 30 62 Wait for 25.000 minute(s)
- 63 Repeat from step 61, 7 times

64 Empty RB2_1to96 for 3.000 minute(s)
65 Goto ChemFile WASH_DMF.CHM, line 1
66 Pause
67
5 68 Goto ChemFile DEPROTEC.CHM, line 1
69 Goto ChemFile WASH_DMF.CHM, line 1
70
71 Pause
72
10 73 REM N-terminalkobling starter her
74 Dispense Sequence C:\ACT\displist\N_56789.DSP with 500µl to RB2_1to96
rack using DMF
75 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
76 Transfer 500µl from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
15 77 Transfer 68µl from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
78 Dispense System Fluid Dualarms_1+4* 500µl to RB2_1to96 [1-96]
79 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
80 Wait for 25.000 minute(s)
81 Repeat from step 79, 20 times
20 82 Empty RB2 1to96 for 3.000 minute(s)
83 Goto ChemFile WASH_DMF.CHM, line 1
84
85 REM N-terminal. Anden kobling
86 Dispense Sequence C:\ACT\displist\N_56789.DSP with 125µl to RB2_1to96
25 rack using DMF
87 Mix "RB2_1to96" for 1.00 minutes at 600 rpm(s)
88 Transfer 125µl from REAGENT_3[1] (HATU) to RB2_1to96 [1-96] using DMF
89 Transfer 20µl from Monomer1to36 [10] (DIEA) to RB2_1to96 [1-96] using DMF
90 Dispense System Fluid Dualarms_1+4* 1250µl to RB2_1to96 [1-96]
30 91 Mix "RB2_1to96" for 5.00 minutes at 750 rpm(s)
92 Wait for 25.000 minute(s)

- 93 Repeat from step 91, 7 times
94 Empty RB2 1to96 for 3.000 minute(s)
95 Goto ChemFile WASH_DMF.CHM, line 1
96 Goto ChemFile WASH_DCM.CHM, line 1
5 97
-

The building blocks were selected from the following groups:

- 10 [Building block 1]: N-Phenethyl-PAL, N-(4-Pyridyl)ethyl-PAL, N-((S)- 2-Hydroxypropyl)-PAL, N-(2,2-Dimethyl-3-hydroxypropyl)-PAL and N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL.
- 15 [Building block 2]: Fmoc-N-Me-D-Phe(4-F)-OH and Fmoc-N-Me-D-Phe(3,4-F,F)-OH.
- [Building block 3]: Fmoc-N-Me-D-Nal-OH and Fmoc-N-Me-D-Phe(4-Phe)-OH.
- 20 [Building block 4]: Boc-AMB-OH, Boc-ADH-OH, Boc-MAMH-OH, Boc-RPMA-OH and Boc-AEHA-OH.

25

See Table 2

EXAMPLES 354-533

The following 180 compounds were synthesized in parallel as individual entities analogously to example 158 on an Advanced ChemTech Model 384 HTS using
5 the following ChemFiles to control the operation of the synthesizer (Advanced ChemTech Operator's Manual, version 1.2 July 1996, pp. 4-13):

ChemFile C:\ACT\CHEMFILE4PETER.CHM Page 1

10

- 1 Flush Arm1 with DMF and THF, Arm2 with DCM and DMF4
- 2 Empty RB3_1to96 for 3.000 minute(s)
- 3 Empty RB4_1to96 for 3.000 minute(s)
- 15 4
- 5 Dispense System Fluid Dualarms_1+4* 1500µl to RB3_1to96[1-96]
- 6 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 7 Dispense System Fluid Dualarms_1+4* 1500µl to RB4_1to96[1-96]
- 8 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 20 9 Empty RB3_1to96 for 3.000 minute(s)
- 10 Empty RB4_1to96 for 3.000 minute(s)
- 11
- 12 REM !! SYNTSESTART HER !!
- 13
- 25 14 REM Aminosyre 1
- 15 Dispense Sequence C:\ACT\displist\A3_3.DSP with 500µl to RB3_1to96 rack using DMF
- 16 Dispense Sequence C:\ACT\displist\A4_3.DSP with 500µl to RB3_1to96 rack using DFM
- 30 17 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 18 Dispense Sequence C:\ACT\displist\A1A2_4.DSP with 500µl to RB4_1to96 rack using DMF

- 19 Dispense Sequence C:\ACT\displist\A3_4.DSP with 500µl to RB4_1to96 rack using DMF
- 20 Dispense Sequence C:\ACT\displist\A4_4.DSP with 500µl to RB4_1to96 rack using DMF
- 5 21 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 22 Transfer 500µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
- 23 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 24 Transfer 500µl from REAGENT_3 [1] (HATU) to RB4_1to96 [1-96] using DMF4
- 10 25 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 26 Dispense System Fluid Dualarms_1+4* 500µl to RB3_1to96 [1-96]
- 27 Dispense System Fluid Dualarms_1+4* 500µl to RB4_1to96 [1-96]
- 28 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF
- 15 29 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
- 30 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF4
- 31 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
- 32 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
- 20 33 Wait for 25.000 minute(s)
- 34 Repeat from step 31, 31 times
- 35 Empty RB3_1to96 for 3.000 minute(s)
- 36 Empty RB4_1to96 for 3.000 minute(s)
- 37 Goto ChemFile WASH_DMF.CHM, line 1
- 25 38
- 39 REM Anden kobling 1ste AA
- 40 Dispense Sequence C:\ACT\displist\A3_3.DSP with 125µl to RB3_1to96 rack using DMF
- 41 Dispense Sequence C:\ACT\displist\A4_3.DSP with 125µl to RB3_1to96 rack
- 30 using DMF
- 42 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)

- 43 Dispense Sequence C:\ACT\displist\A1A2_4.DSP with 125µl to RB4_1to96 rack using DMF
- 44 Dispense Sequence C:\ACT\displist\A3_4.DSP with 125µl to RB4_1to96 rack using DMF
- 5 45 Dispense Sequence C:\ACT\displist\A4_4.DSP with 125µl to RB4_1to96 rack using DMF
- 46 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 47 Transfer 125µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
- 48 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 10 49 Transfer 125µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4
- 50 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 51 Dispense System Fluid Dualarms_1+4* 1250µl to RB3_1to96 [1-96]
- 52 Dispense System Fluid Dualarms_1+4* 1250µl to RB4_1to96 [1-96]
- 15 53 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF
- 54 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
- 55 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF4
- 20 56 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
- 57 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
- 58 Wait for 25.000 minute(s)
- 59 Repeat from step 56, 7 times
- 60 Empty RB3_1to96 for 3.000 minute(s)
- 25 61 Empty RB4_1to96 for 3.000 minute(s)
- 62
- 63 Goto ChemFile WASH_DMF.CHM, line 1
- 64 Goto ChemFile DEPROTEC.CHM, line 1
- 65 Goto ChemFile WASH_DMF.CHM, line 1
- 30 66
- 67 Pause

- 68
- 69 REM Start anden AA-kobling
- 70 Dispense Sequence C:\ACT\displist\B1_3.DSP with 500µl to RB3_1to96 rack using DMF
- 5 71 Dispense Sequence C:\ACT\displist\B2_3.DSP with 500µl to RB3_1to96 rack using DMF
- 72 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 73 Dispense Sequence C:\ACT\displist\B1_4.DSP with 500µl to RB4_1to96 rack using DMF
- 10 74 Dispense Sequence C:\ACT\displist\B2_4.DSP with 500µl to RB4_1to96 rack using DMF
- 75 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 76 Transfer 500µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
- 77 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 15 78 Transfer 500µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4
- 79 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 80 Dispense System Fluid Dualarms_1+4* 500µl to RB3_1to96 [1-96]
- 81 Dispense System Fluid Dualarms_1+4* 500µl to RB4_1to96 [1-96]
- 20 82 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF
- 83 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
- 84 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF4
- 25 85 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
- 86 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
- 87 Wait for 25.000 minute(s)
- 88 Repeat from step 85, 31 times
- 89 Empty RB3_1to96 for 3.000 minute(s)
- 30 90 Empty RB4_1to96 for 3.000 minute(s)
- 91 Goto ChemFile WASH_DMF.CHM, line 1

- 92
- 93 REM Anden kobling anden AA
- 94 Dispense Sequence C:\ACT\displist\B1_3.DSP with 125µl to RB3_1to96 rack using DMF
- 5 95 Dispense Sequence C:\ACT\displist\B2_3.DSP with 125µl to RB3_1to96 rack using DMF
- 96 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 97 Dispense Sequence C:\ACT\displist\B1_4.DSP with 125µl to RB4_1to96 rack using DMF
- 10 98 Dispense Sequence C:\ACT\displist\B2_4.DSP with 125µl to RB4_1to96 rack using DMF
- 99 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 100 Transfer 125µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
- 101 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
- 15 102 Transfer 125µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4
- 103 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
- 104 Dispense System Fluid Dualarms_1+4* 1250µl to RB3_1to96 [1-96]
- 105 Dispense System Fluid Dualarms_1+4* 1250µl to RB4_1to96 [1-96]
- 20 106 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF
- 107 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
- 108 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using DMF
- 25 109 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
- 110 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
- 111 Wait for 25.000 minute(s)
- 112 Repeat from step 109, 7 times
- 113 Empty RB3_1to96 for 3.000 minute(s)
- 30 114 Empty RB4_1to96 for 3.000 minute(s)
- 115

- 116 Goto ChemFile WASH_DMF.CHM, line 1
117 Goto ChemFile DEPROTEC.CHM, line 1
118 Goto ChemFile WASH_DMF.CHM, line 1
119
5 120 Pause
121
122 REM N-terminal kobling start
123 Dispense Sequence C:\ACT\displist\N_3.DSP with 500µl to RB3_1to96 rack using DMF
10 124 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
125 Dispense Sequence C:\ACT\displist\N_4.DSP with 500µl to RB4_1to96 rack using DMF
126 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
127 Transfer 500µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
15 128 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
129 Transfer 500µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using DMF4
130 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
131 Dispense System Fluid Dualarms_1+4* 500µl to RB3_1to96 [1-96]
20 132 Dispense System Fluid Dualarms_1+4* 500µl to RB4_1to96 [1-96]
133 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using DMF
134 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
135 Transfer 68µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using
25 DMF4
136 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
137 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
138 Wait for 25.000 minute(s)
139 Repeat from step 136, 31 times
30 140 Empty RB3_1to96 for 3.000 minute(s)
141 Empty RB4_1to96 for 3.000 minute(s)

142 Goto ChemFile WASH_DMF.CHM, line 1
143
144 REM
145 Dispense Sequence C:\ACT\displist\N_3.DSP with 125µl to RB3_1to96 rack
5 using DMF
146 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
147 Dispense Sequence C:\ACT\displist\N_4.DSP with 125µl to RB4_1to96 rack
using DMF
148 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
10 149 Transfer 125µl from REAGENT_3[1] (HATU) to RB3_1to96 [1-96] using DMF
150 Mix "RB3_1to96" for 30 seconds at 300 rpm(s)
151 Transfer 125µl from REAGENT_3[1] (HATU) to RB4_1to96 [1-96] using
DMF4
152 Mix "RB4_1to96" for 30 seconds at 300 rpm(s)
15 153 Dispense System Fluid Dualarms_1+4* 1250µl to RB3_1to96 [1-96]
154 Dispense System Fluid Dualarms_1+4* 1250µl to RB4_1to96 [1-96]
155 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB3_1to96 [1-96] using
DMF
156 Mix "RB3_1to96" for 1.00 minutes at 600 rpm(s)
20 157 Transfer 20µl from Monomer1to36 [16] (DIEA) to RB4_1to96 [1-96] using
DMF4
158 Start mixing "RB3_1to96" for 5.00 minutes at 600 rpm(s)
159 Mix "RB4_1to96" for 5.00 minutes at 600 rpm(s)
160 Wait for 25.000 minute(s)
25 161 Repeat from step 158, 7 times
162 Empty RB3_1to96 for 3.000 minute(s)
163 Empty RB4_1to96 for 3.000 minute(s)
164 Goto ChemFile WASH_DMF.CHM, line 1
165

The building blocks were selected from the following groups:

[Building block 1]: N-Phenethyl-PAL, N-(4-Pyridyl)ethyl-PAL, N-((S)- 2-
5 Hydroxypropyl)-PAL, N-(2,2-Dimethyl-3-hydroxypropyl)-PAL and N-((1-Methylpyrrolidin-2-yl)ethyl)-PAL.

[Building block 2]: Fmoc-N-Me-D-Phe-OH and Fmoc-N-Me-D-ThiAla-OH.

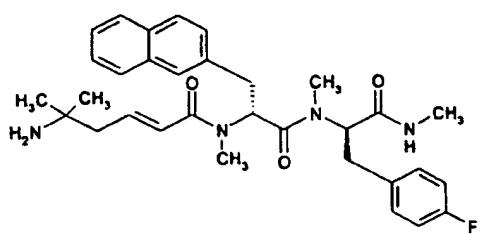
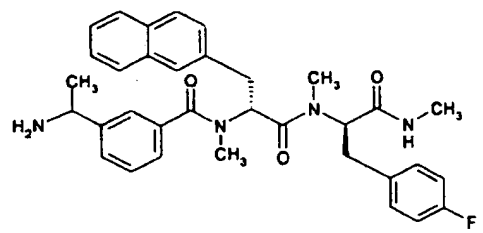
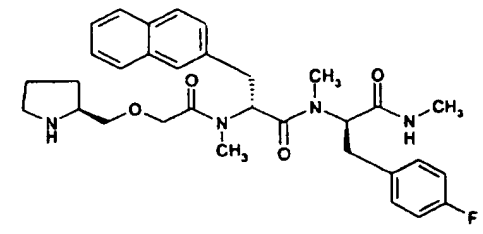
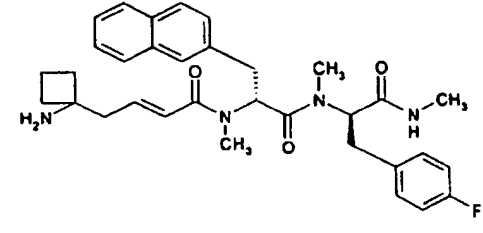
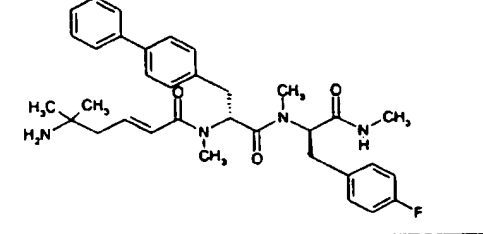
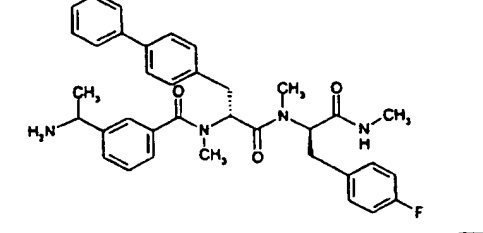
10

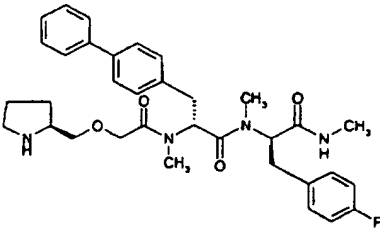
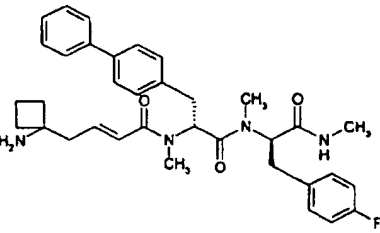
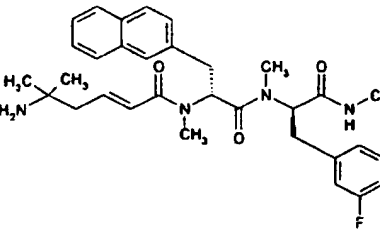
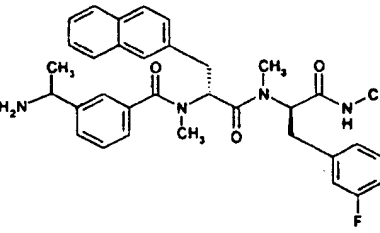
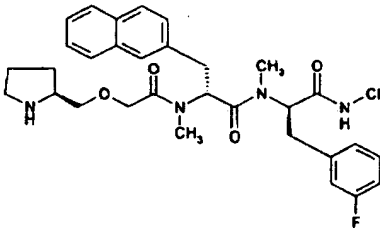
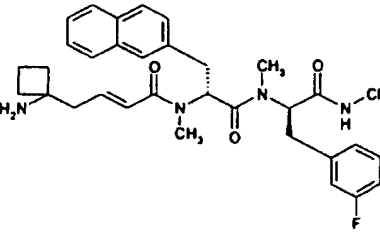
[Building block 3]: Fmoc-N-Me-D-Nal-OH and Fmoc-N-Me-D-Phe(4-Phe)-OH.

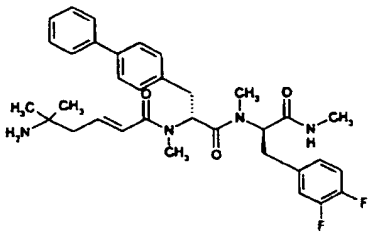
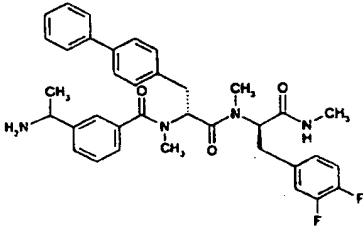
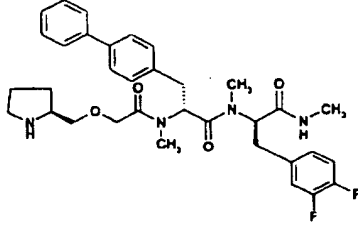
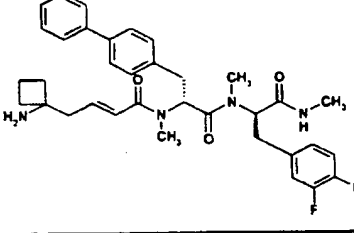
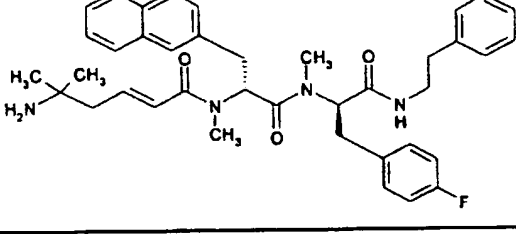
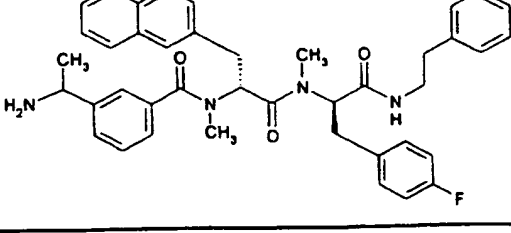
[Building block 4]: Boc-AMH-OH, Boc-ACBMA-OH, Boc-RPMA-OH, Boc-AEB-
15 OH, Boc-AMB-OH, Boc-ADH-OH, Boc-MAMH-OH, Boc-RPMA-OH and Boc-AEHA-OH.

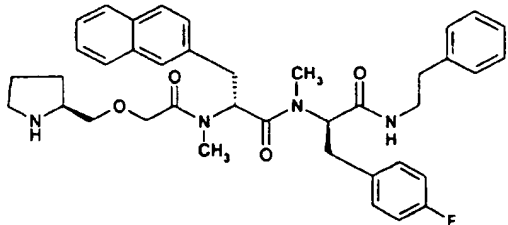
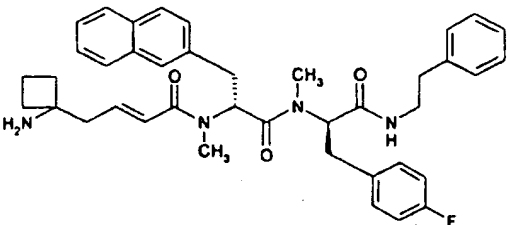
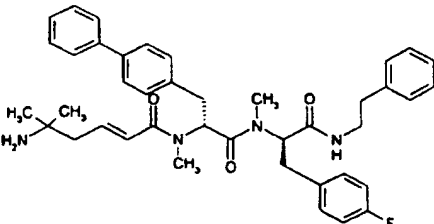
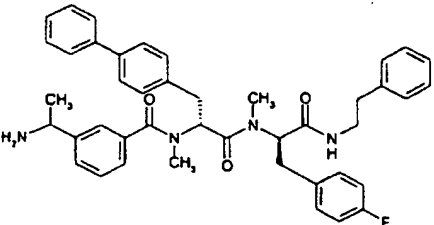
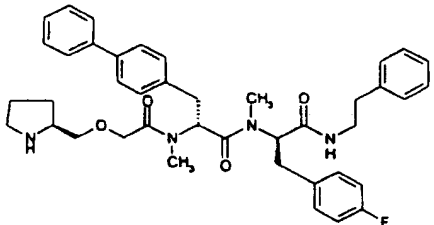
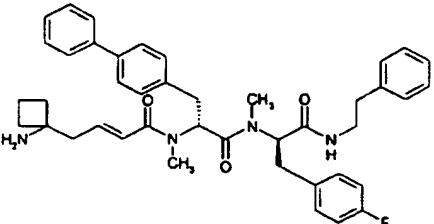
See Table 3

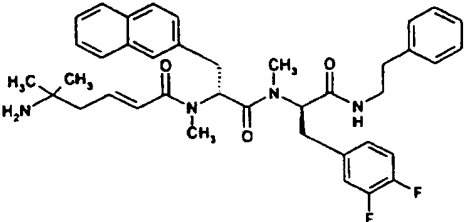
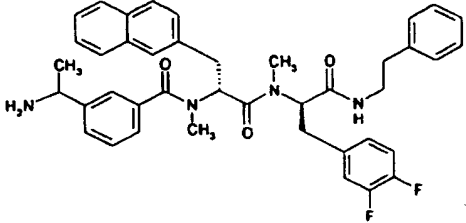
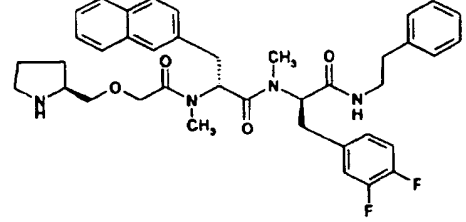
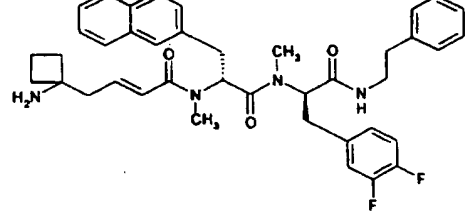
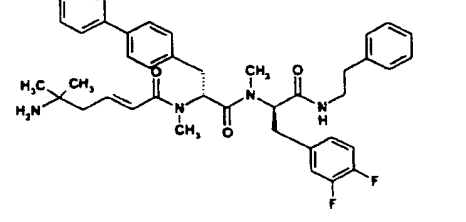
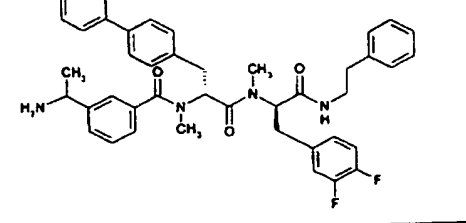
Table 1

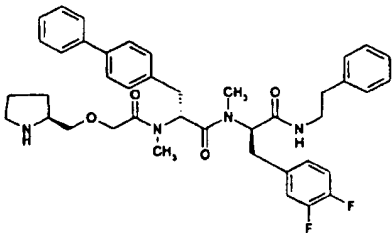
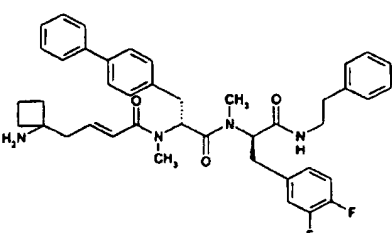
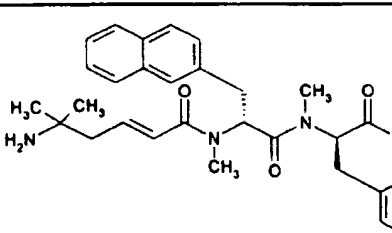
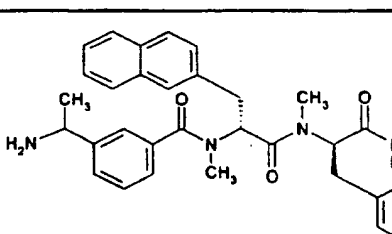
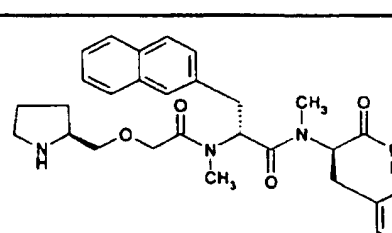
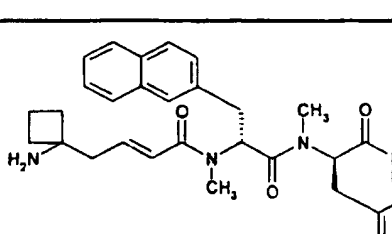
Example	Structure	MW	HPLC	LCMS
158		546,7	9,91	546,8
159		568,7	9,68	569,0
160		562,7	9,38	563,0
161		558,7	9,63	559,0
162		572,7	10,11	573,0
163		594,7		

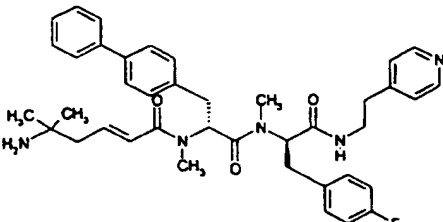
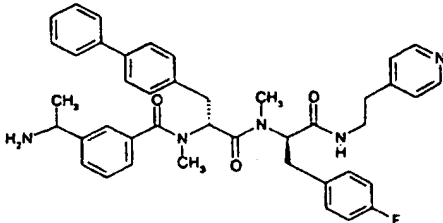
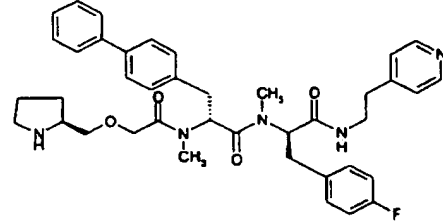
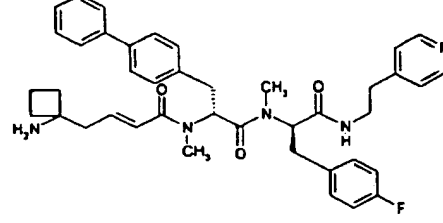
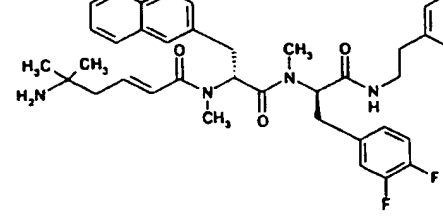
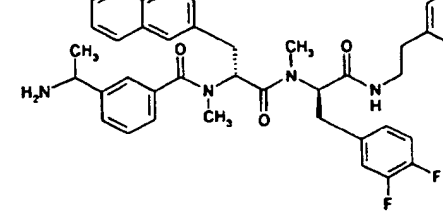
164		588,7	10,02	589,2
165		584,7		
166		564,7	9,68	565,0
167		586,7	9,83	587,2
168		580,7	9,61	581,0
169		576,7		576,8

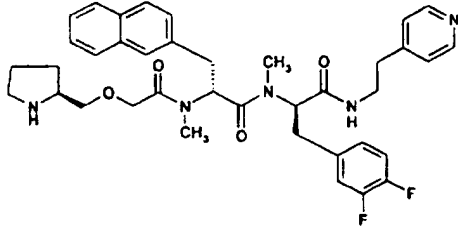
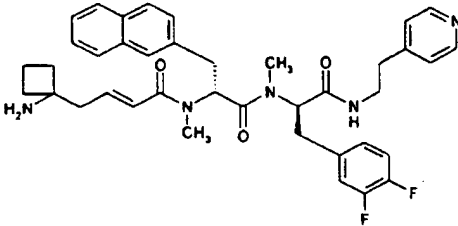
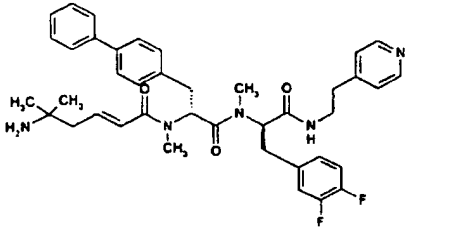
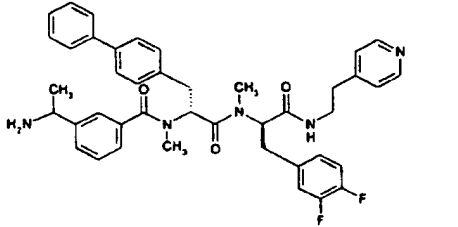
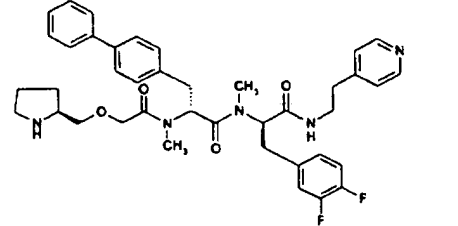
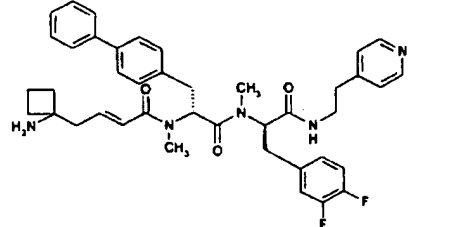
170		590,7		
171		612,7	10,49	613,2
172		606,7	10,26	607,0
173		602,7	10,50	603,0
174		636,8	10,73	637,2
175		658,8	10,97	659,2

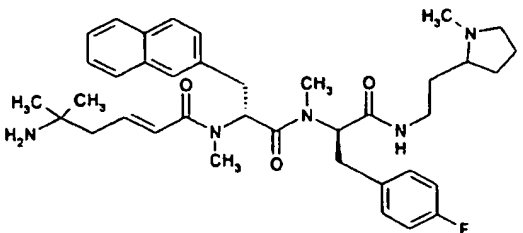
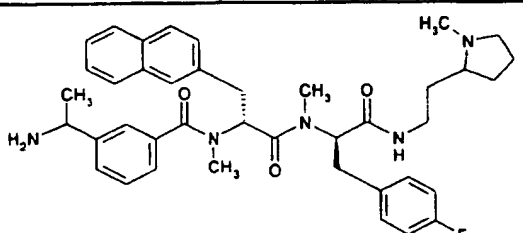
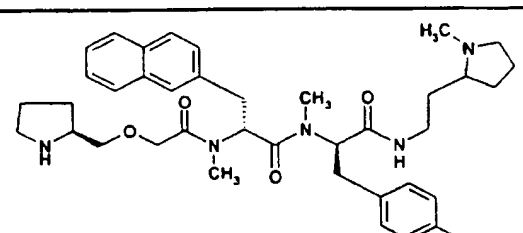
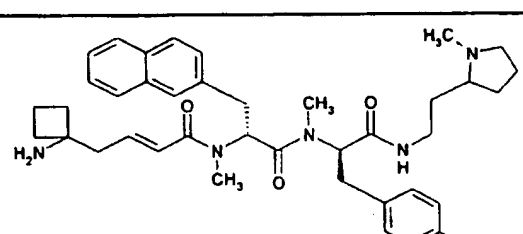
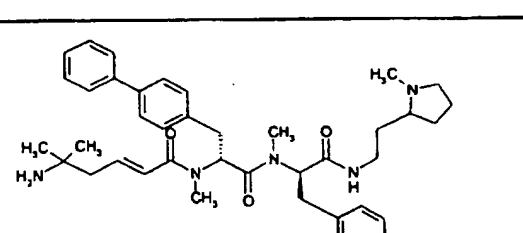
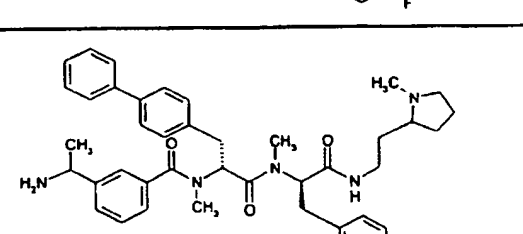
176		652,8	11,07	653,2
177		648,8		
178		662,9	11,56	663,2
179		684,9	11,81	685,0
180		678,9	11,60	679,0
181		674,9	11,95	675,2

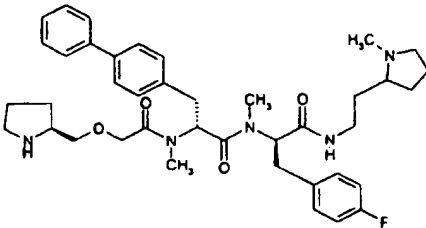
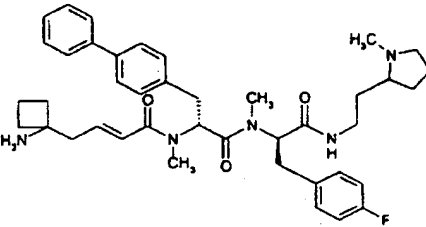
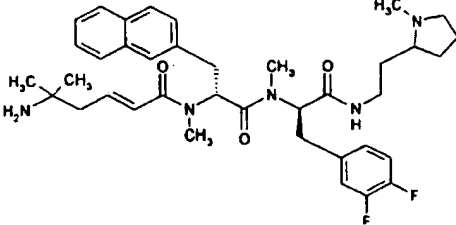
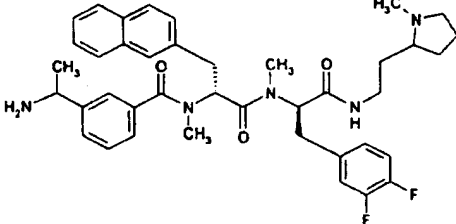
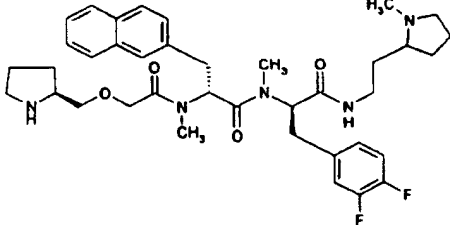
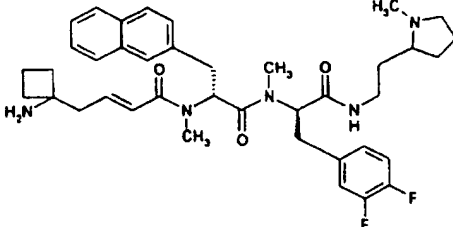
182		654,8	11,28	655,0
183		676,8	11,40	677,2
184		670,8	11,27	672,2
185		666,8	11,44	667,2
186		680,8	11,80	681,0
187		702,9	12,10	702,8

188		696,8	11,97	697,0
189		692,9		
190		637,8	8,06	638,2
191		659,8	8,27	660,0
192		653,8	8,05	654,2
193		649,8	8,33	650,2

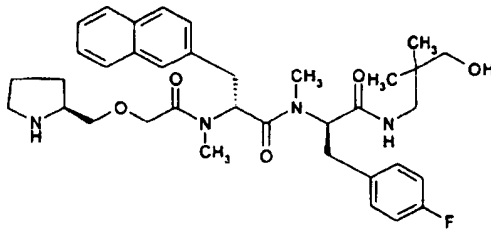
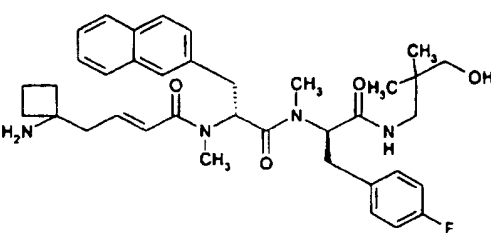
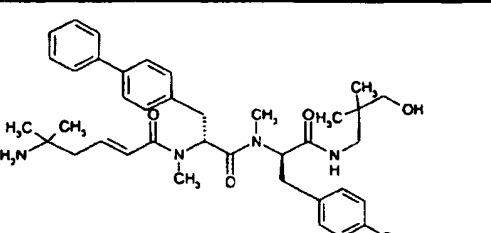
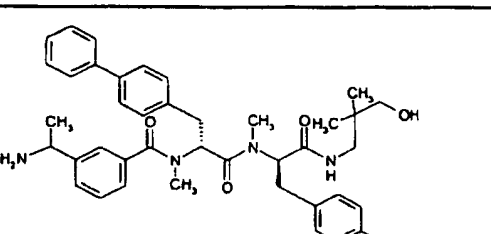
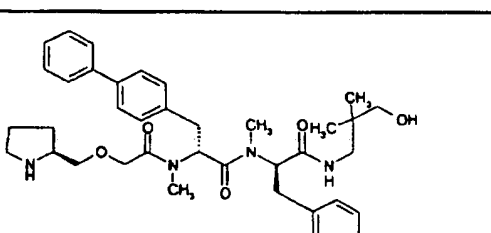
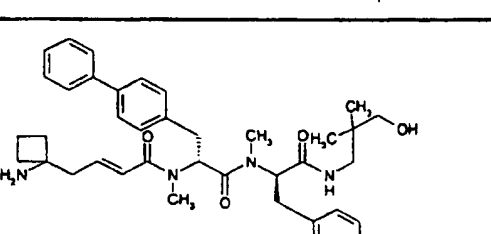
194		663,8	8,44	664,2
195		685,8	8,84	686,0
196		679,8	8,61	680,0
197		675,9		
198		655,8	8,37	656,0
199		677,8	8,45	678,0

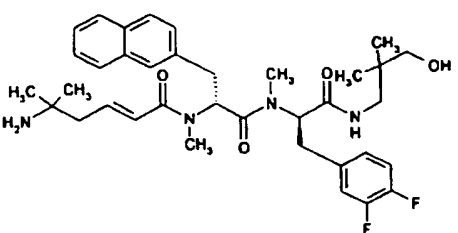
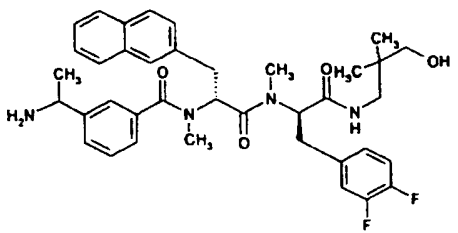
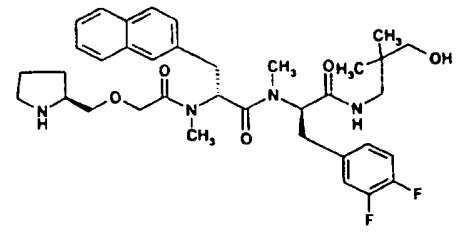
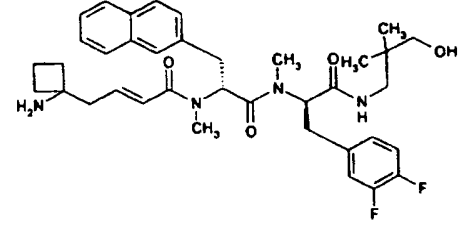
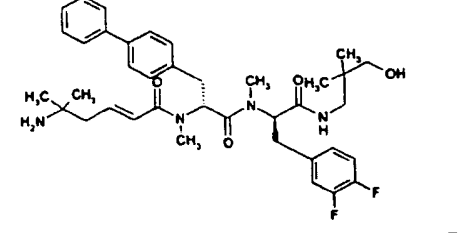
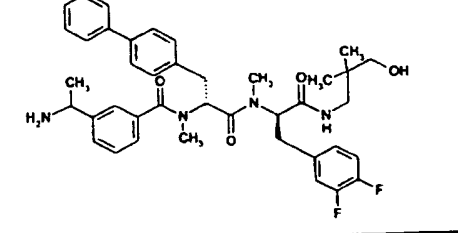
200		671,8	8,26	672,2
201		667,8	8,51	668,0
202		681,8	8,52	682,0
203		703,8	8,63	704,0
204		697,8	8,79	689,2
205		693,8	8,99	

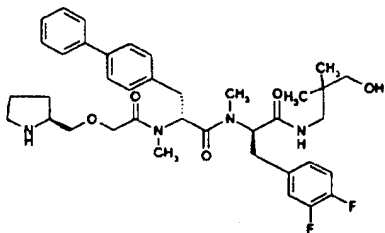
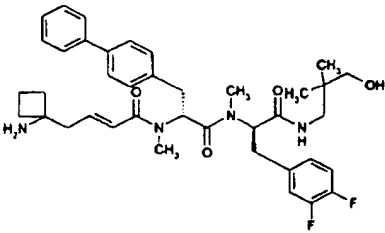
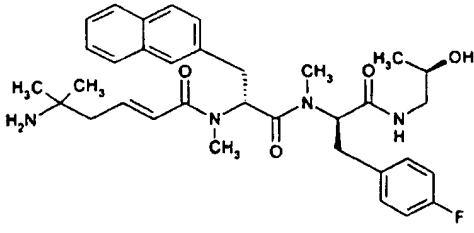
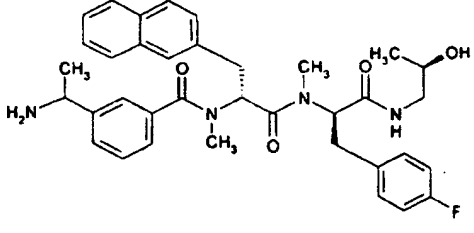
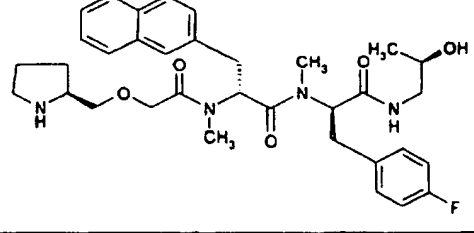
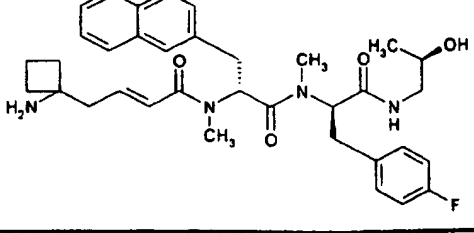
206		643,9	7,95	644,2
207		665,9	8,08	666,2
208		659,9	8,15	660,0
209		655,9	8,35	656,2
210		669,9	8,77	670,2
211		691,9	8,93	692,2

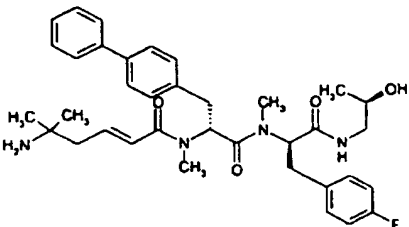
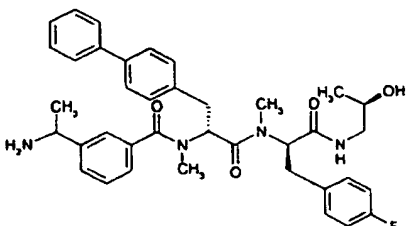
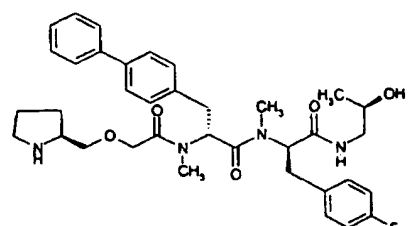
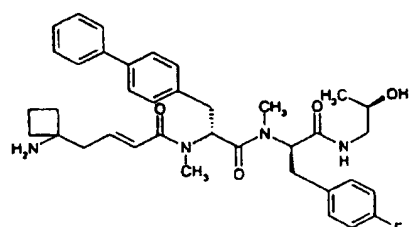
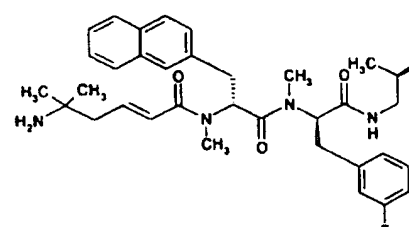
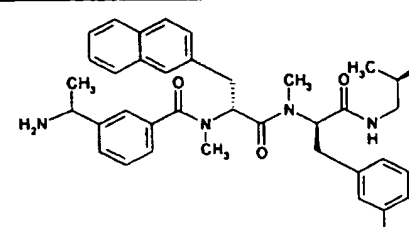
212		685,9	8,70	686,0
213		681,9		
214		661,8	7,88	662,2
215		683,8	8,53	684,0
216		677,8	8,36	678,0
217		673,9		

[illegible]

224		634,8	9,42	635,2
225		630,8	9,98	629,8
226		644,8		
227		666,8	10,78	667,4
228		660,8		
229		656,8		

230		636,8		
231		658,8	9,90	658,0
232		652,8	9,66	653,0
233		648,8		
234		662,8	10,34	663,0
235		684,8		

236		678,8	10,01	679,2
237		674,8		
238		590,7	8,48	591,0
239		612,8	9,52	613,0
240		606,7	9,28	607,0
241		602,8	9,59	603,0

242		616,8	9,05	617,2
243		638,8	8,97	639,0
244		632,8		633,0
245		628,8		629,0
246		608,7	9,12	608,8
247		630,7	9,72	631,0

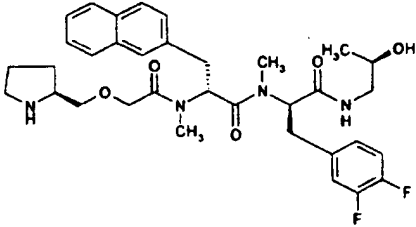
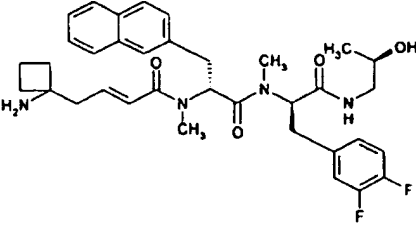
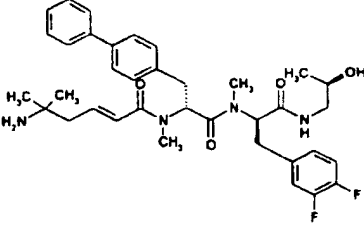
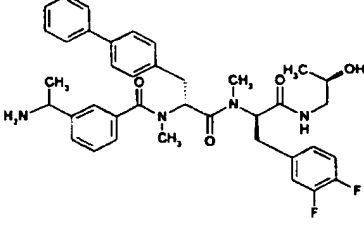
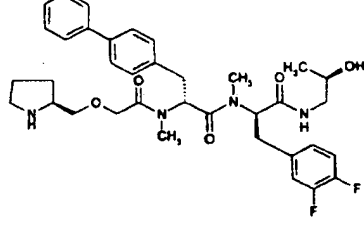
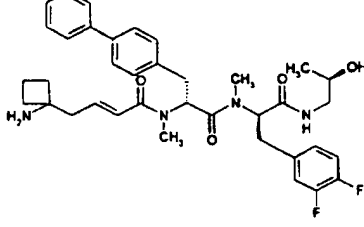
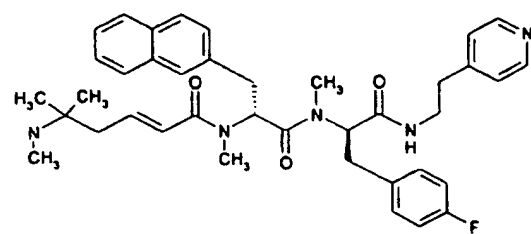
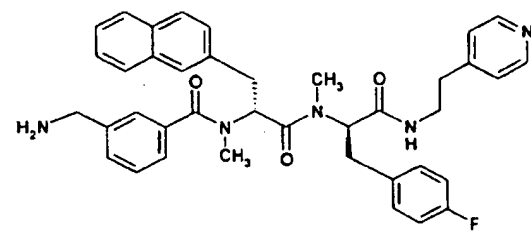
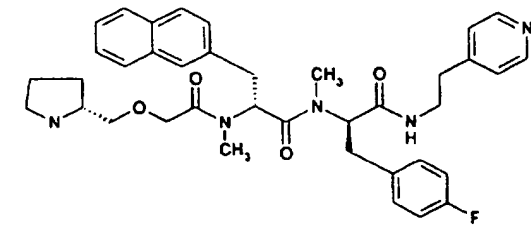
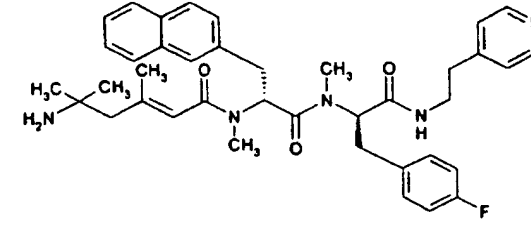
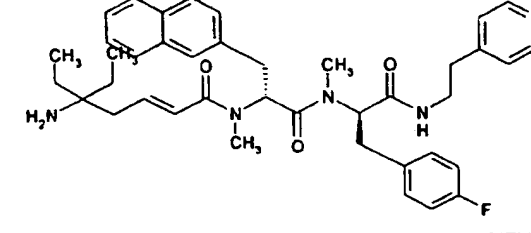
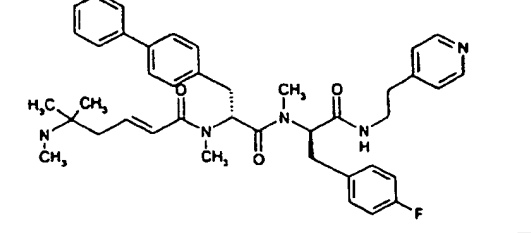
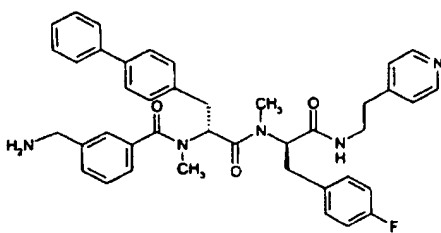
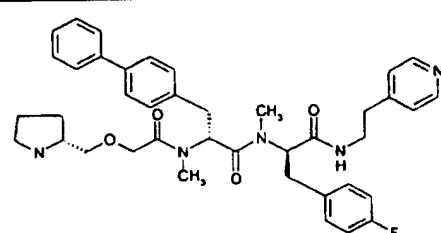
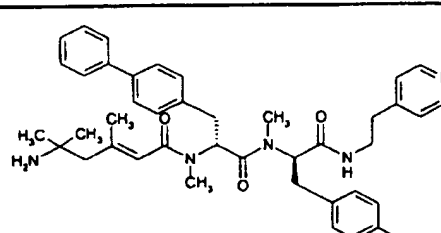
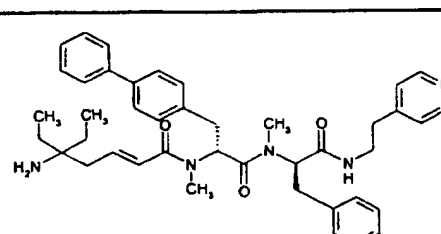
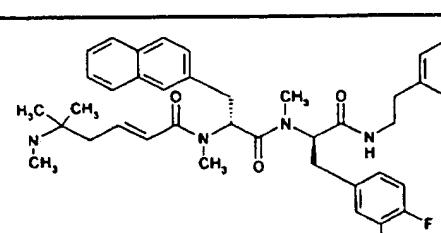
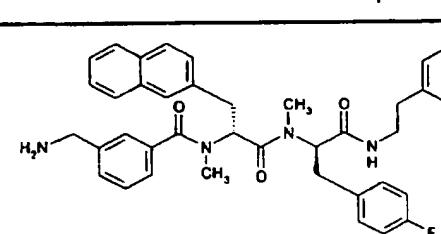
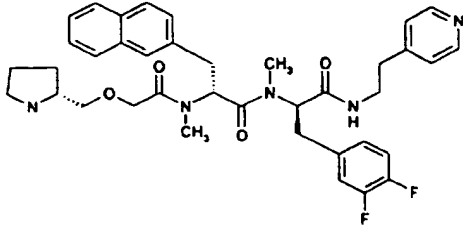
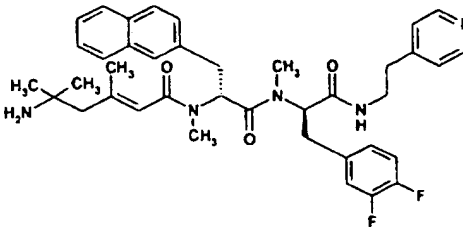
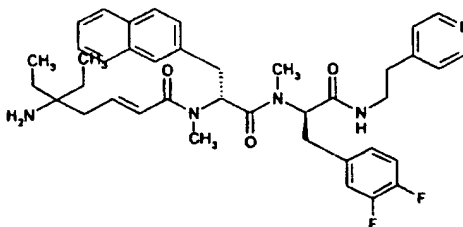
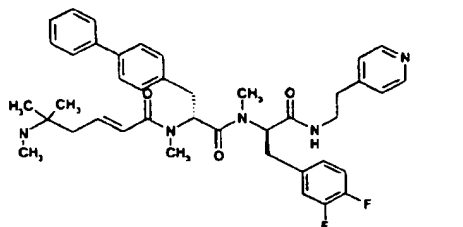
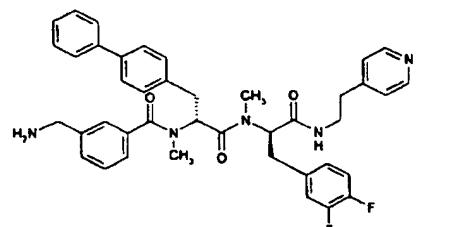
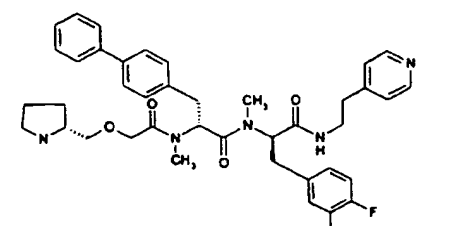
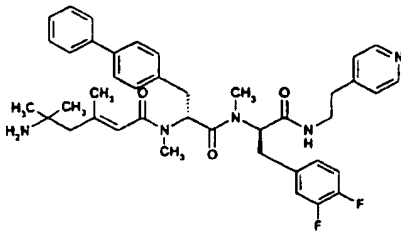
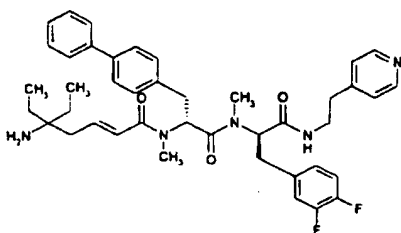
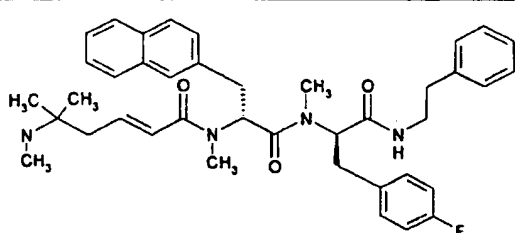
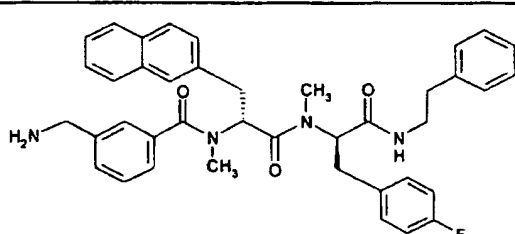
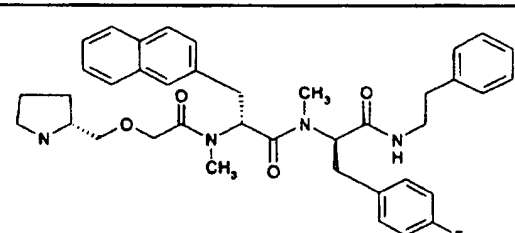
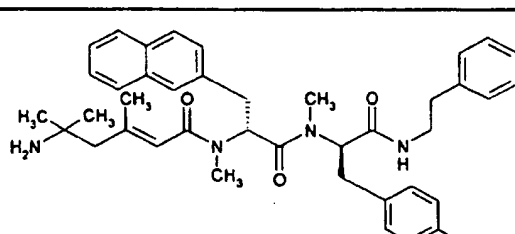
248		624,7	9,51	625,0
249		620,7	9,26	621,0
250		634,8		
251		656,8	9,50	656,8
252		650,8	9,50	651,0
253		646,8	9,48	

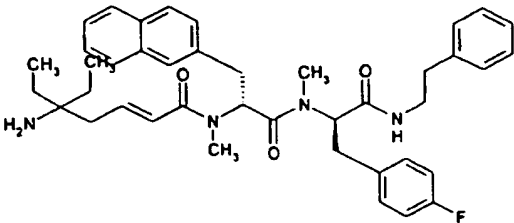
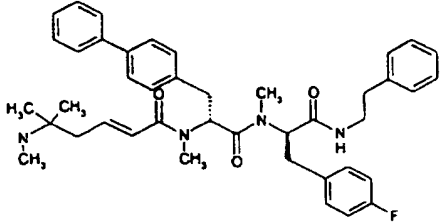
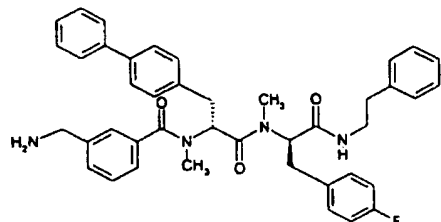
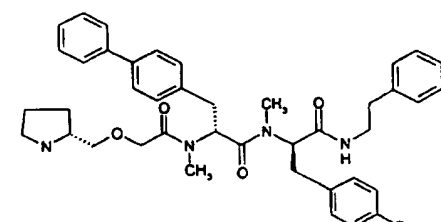
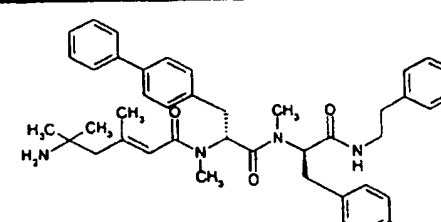
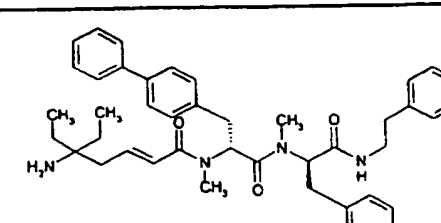
Table 2

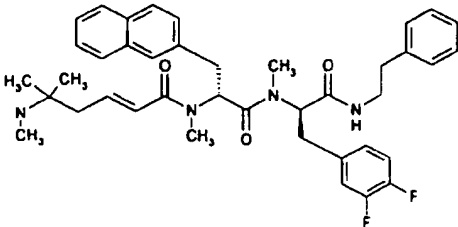
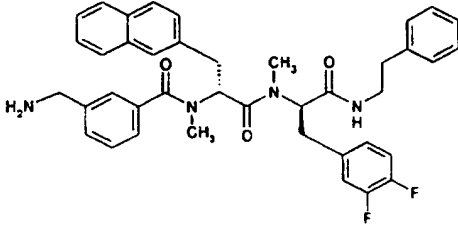
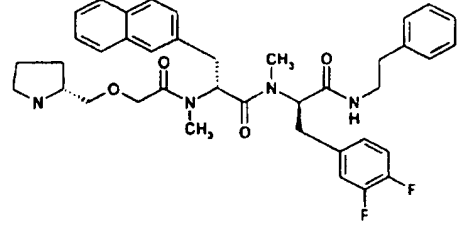
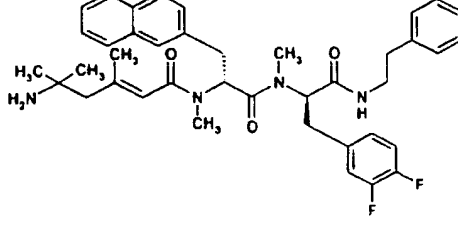
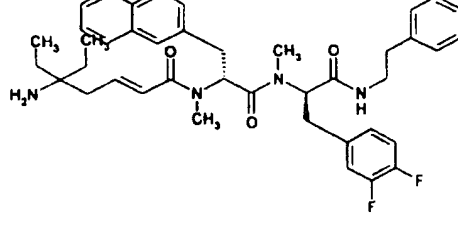
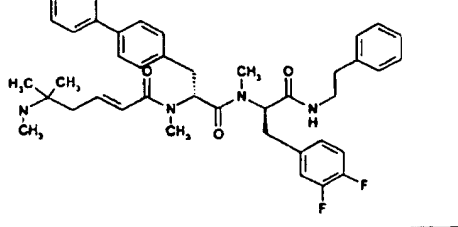
Example	Structure	MW	HPLC	LC-MS
254		651,83		
255		645,78		
256		653,80		
257		651,83		
258		665,86		
259		677,87		

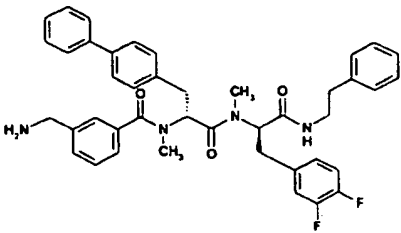
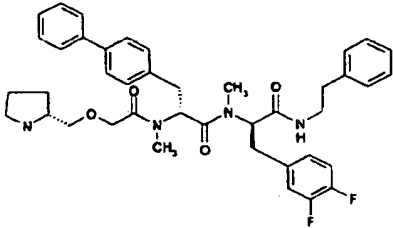
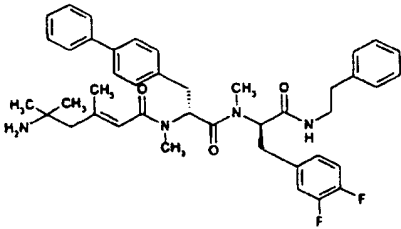
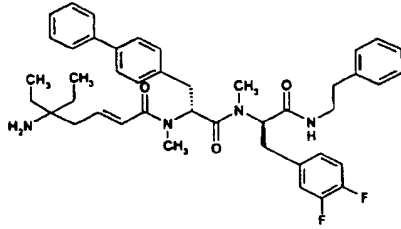
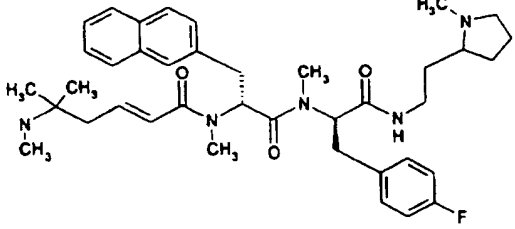
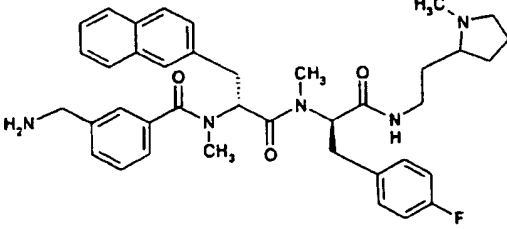
260		671,82		
261		679,84		
262		677,87		
263		691,90		
264		669,82		
265		663,77		

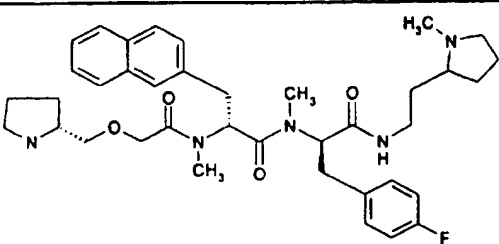
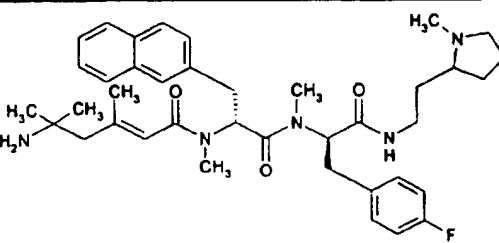
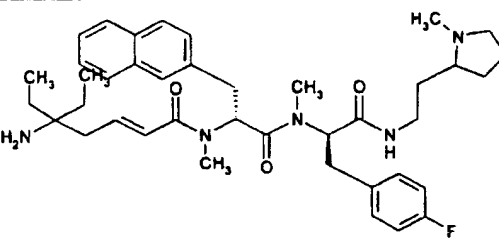
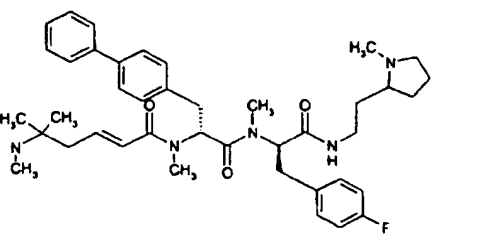
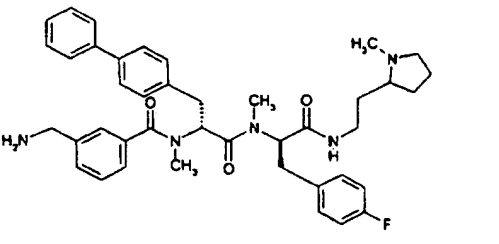
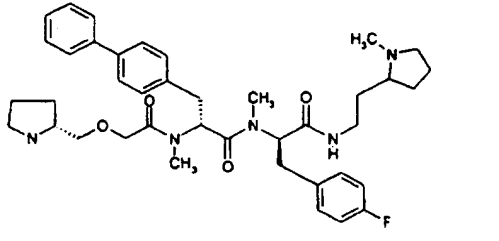
266		671,79		
267		669,82		
268		683,85		
269		695,86		
270		689,81		
271		697,83		

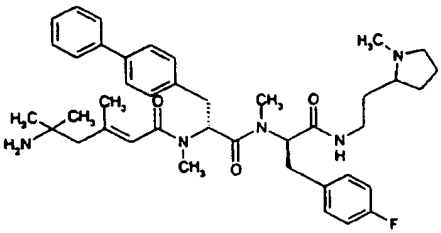
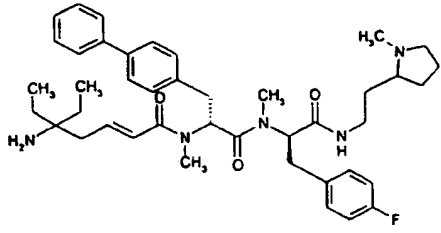
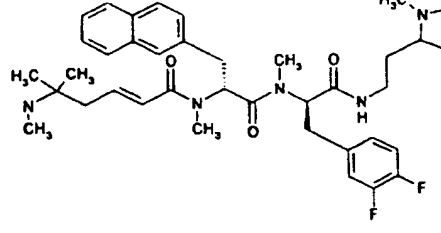
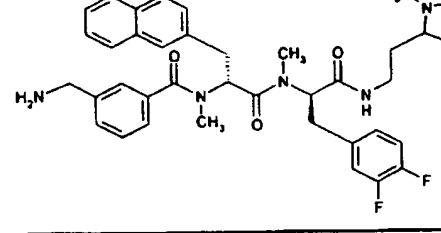
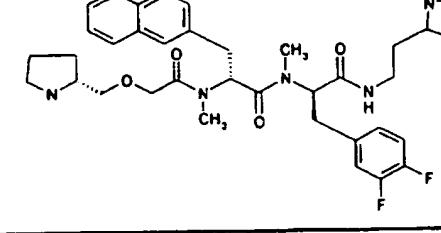
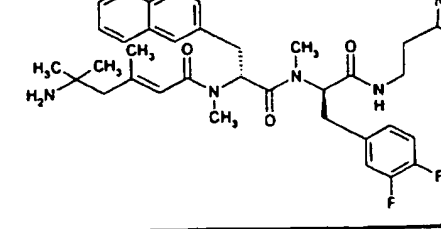
272		695,86		
273		709,89		
274		650,84		
275		644,80		
276		652,82		
277		650,84		

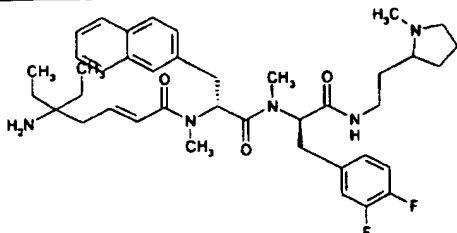
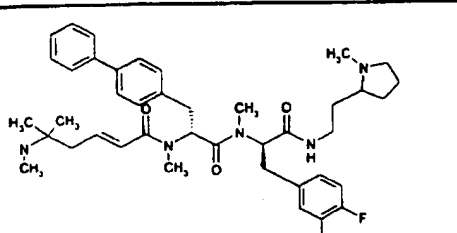
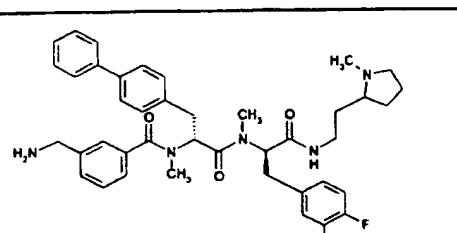
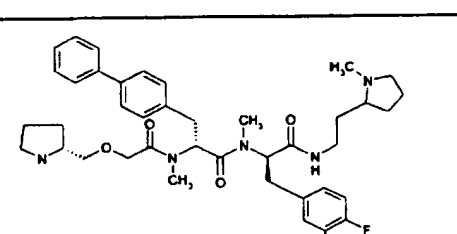
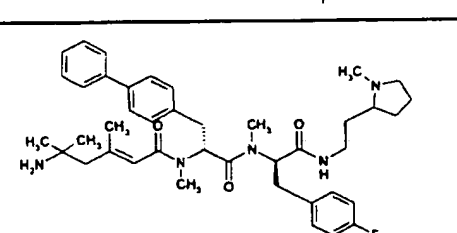
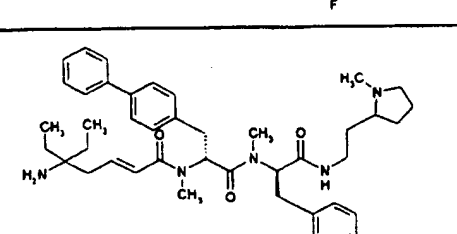
278		664,87		
279		676,88		
280		670,83		
281		678,85		
282		676,88		
283		690,91		

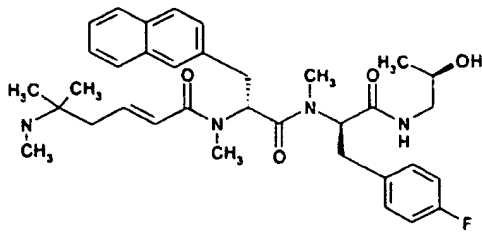
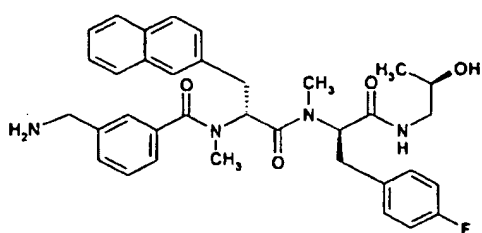
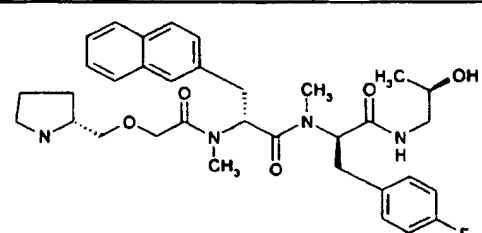
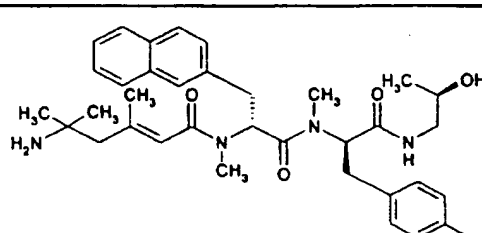
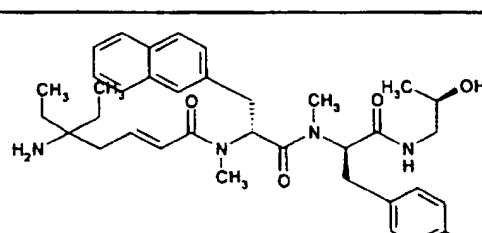
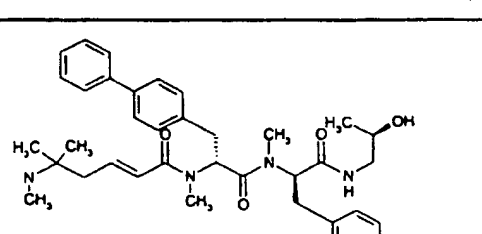
284		668,83		
285		662,79		
286		670,81		
287		668,83		
288		682,86		
289		694,87		

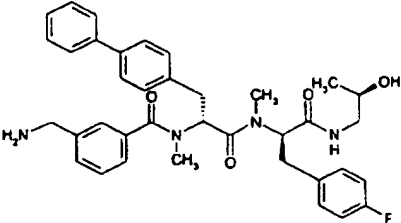
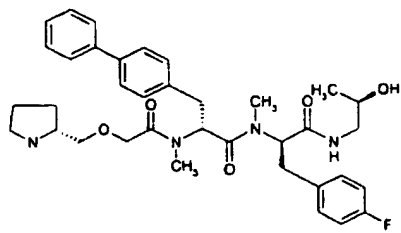
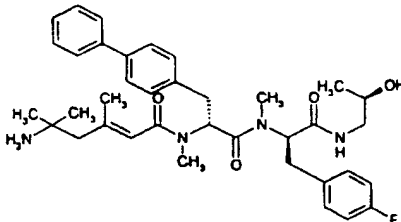
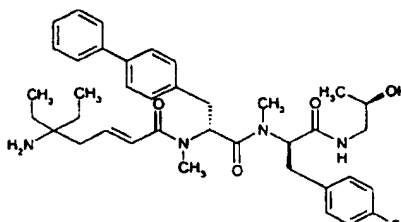
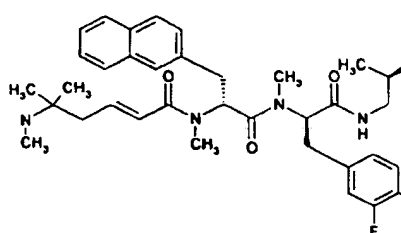
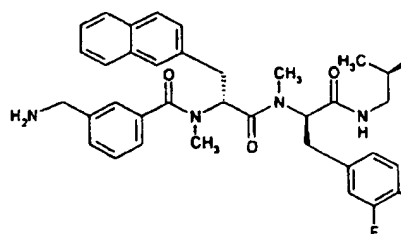
290		688,82		
291		696,84		
292		694,87		
293		708,90		
294		657,88		
295		651,83		

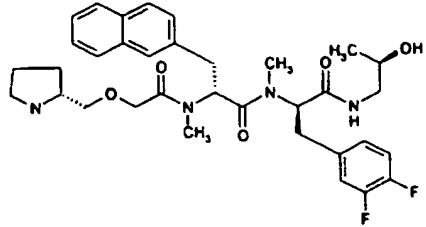
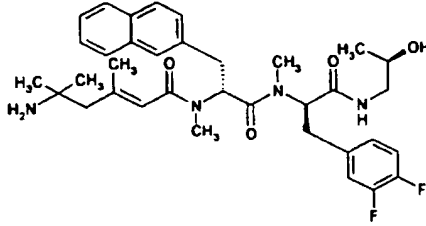
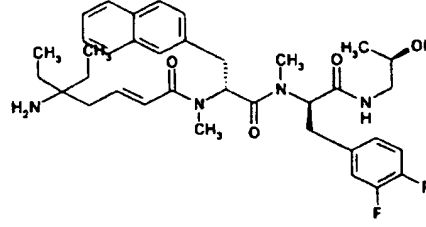
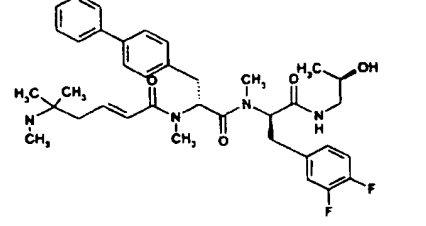
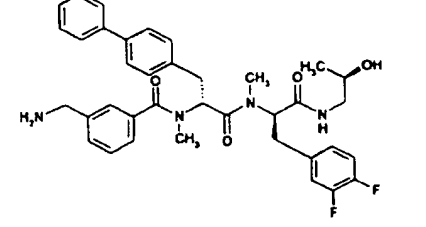
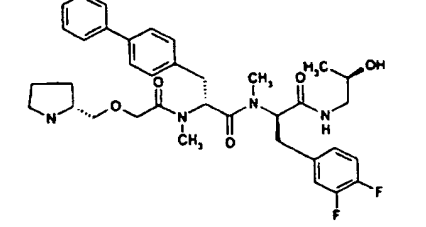
296		659,85		
297		657,88		
298		671,91		
299		683,92		
300		677,87		
301		685,89		

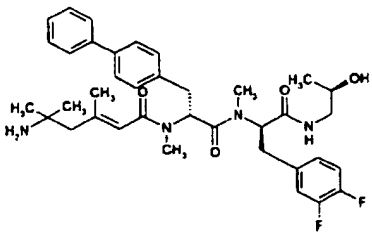
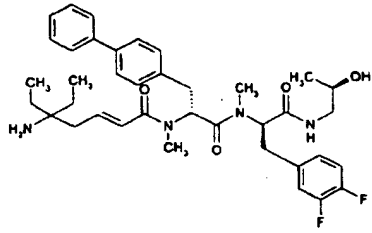
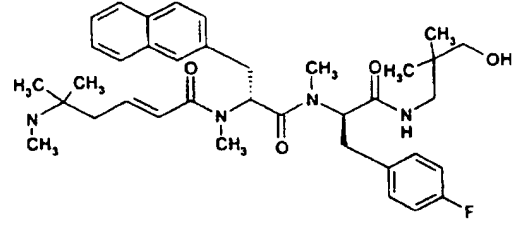
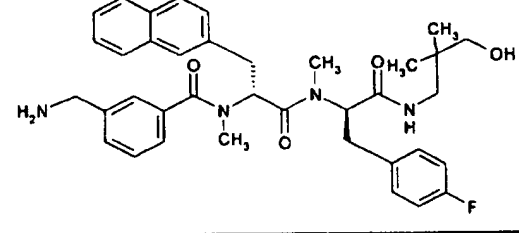
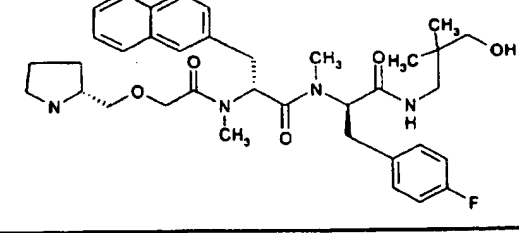
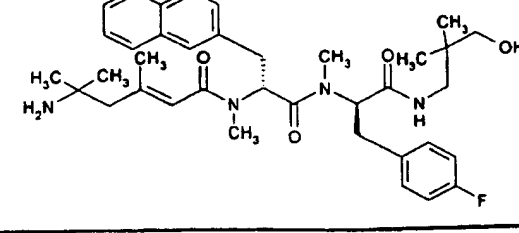
302		683,92		
303		697,94		
304		675,87		
305		669,82		
306		677,84		
307		675,87		

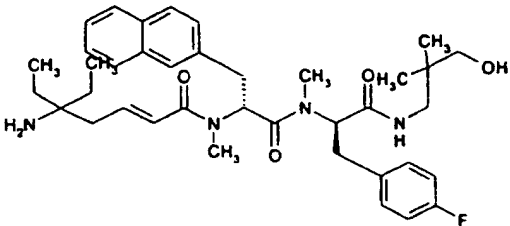
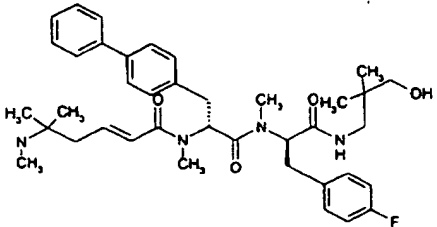
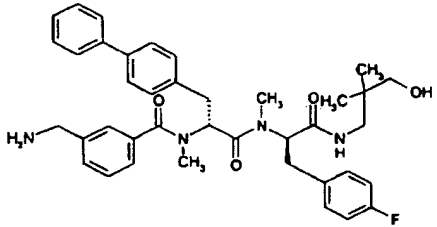
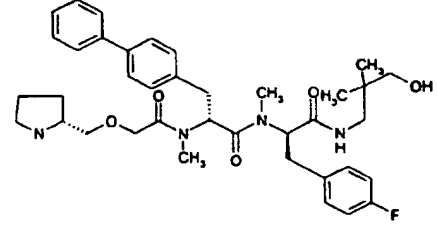
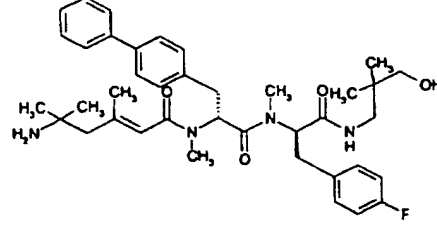
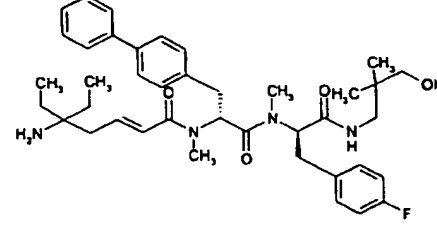
308		689,90		
309		701,91		
310		695,86		
311		703,88		
312		701,91		
313		715,94		

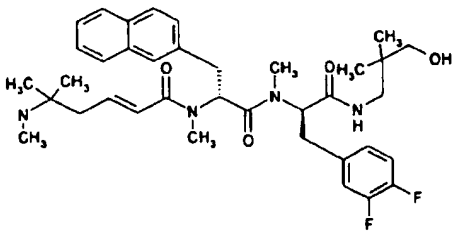
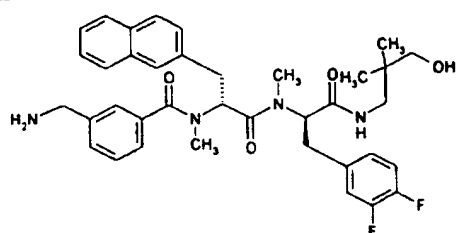
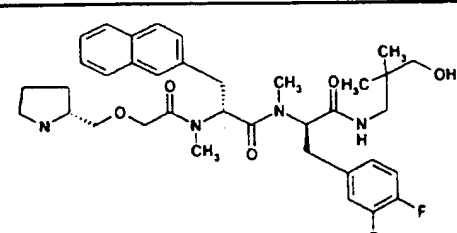
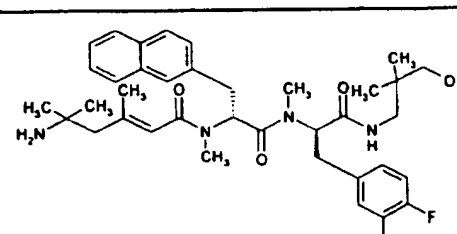
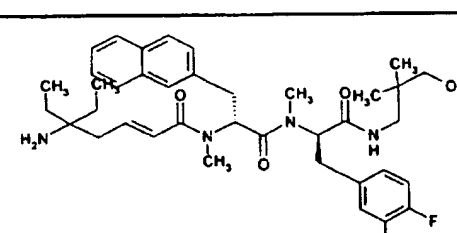
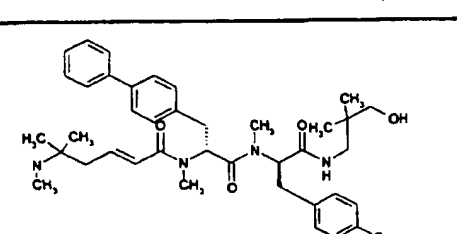
314		604,77		
315		598,72		
316		606,74		
317		604,77		
318		618,80		
319		630,81		

320		624,76		
321		632,78		
322		630,81		
323		644,84		
324		622,76		
325		616,71		

326		624,73		
327		622,76		
328		636,79		
329		648,80		
330		642,75		
331		650,77		

332		648,80		
333		662,83		
334		632,83		
335		626,78		
336		634,80		
337		632,83		

338		646,85		
339		658,86		
340		652,82		
341		660,84		
342		658,86		
343		672,89		

344		650,82		
345		644,77		
346		652,79		
347		650,82		
348		664,84		
349		676,85		

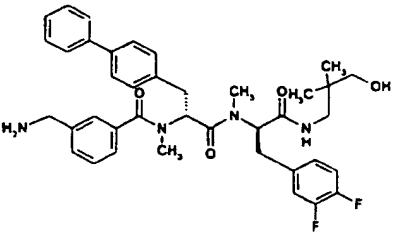
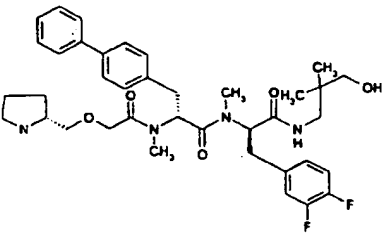
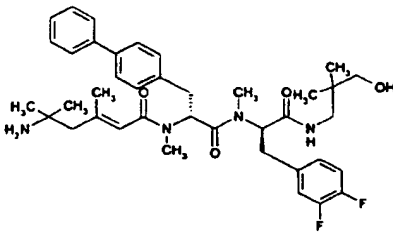
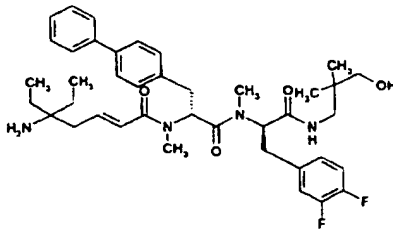
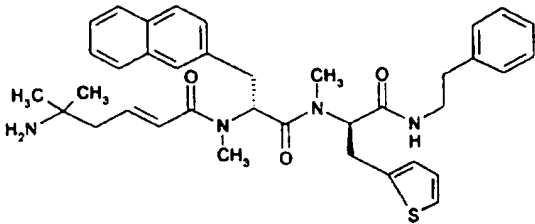
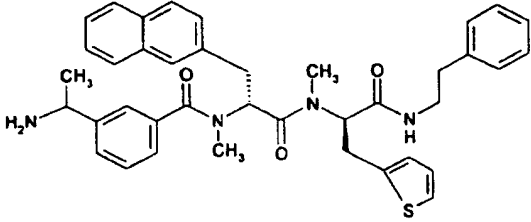
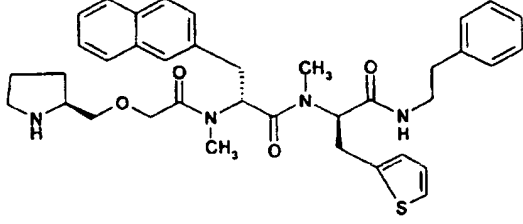
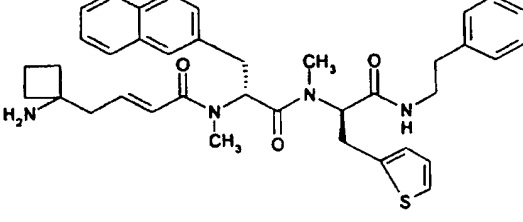
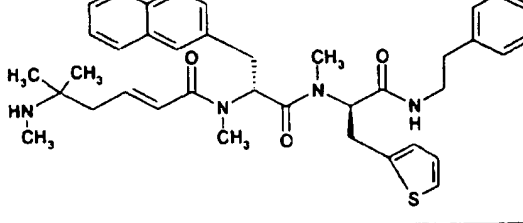
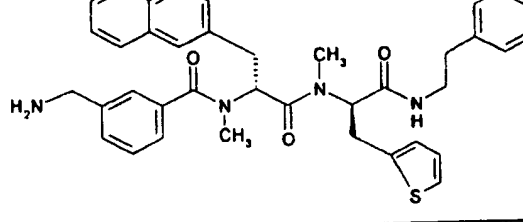
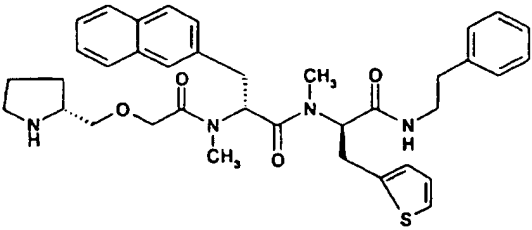
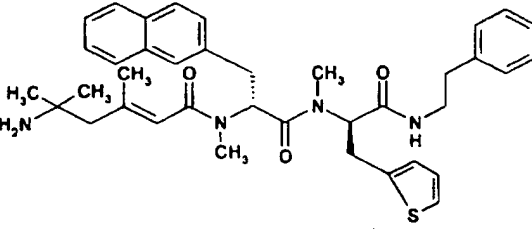
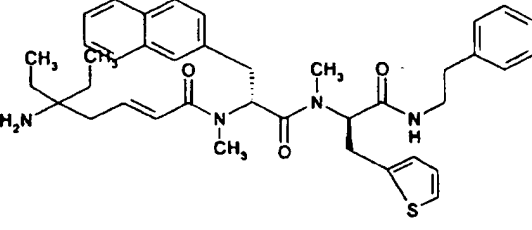
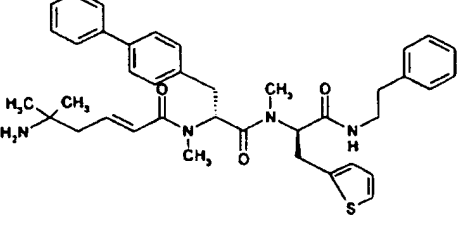
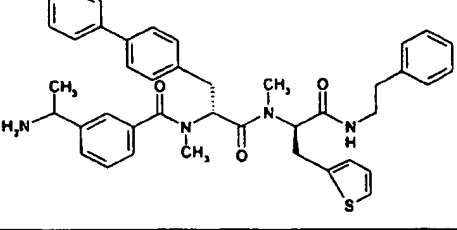
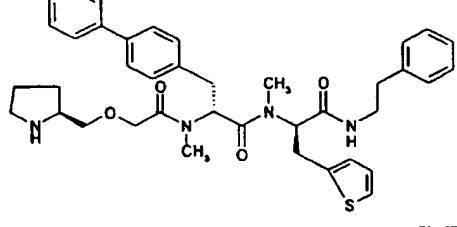
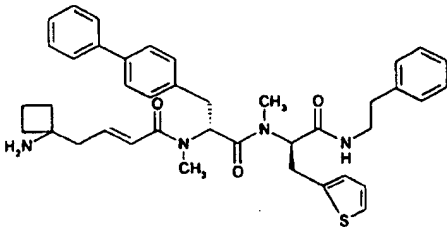
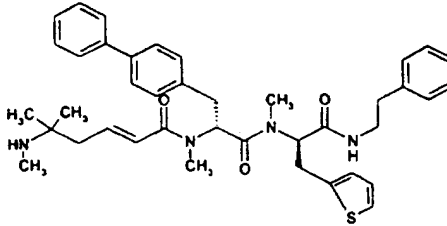
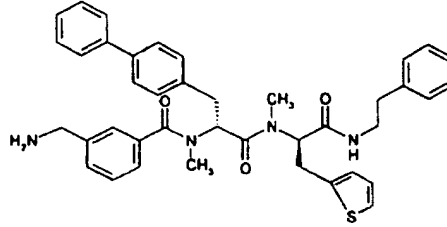
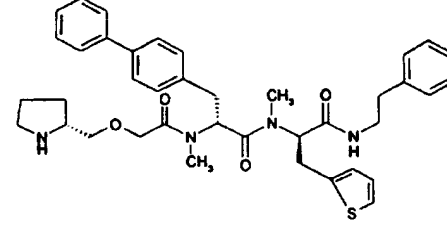
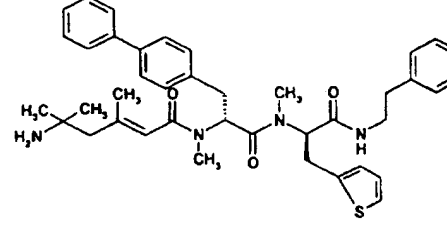
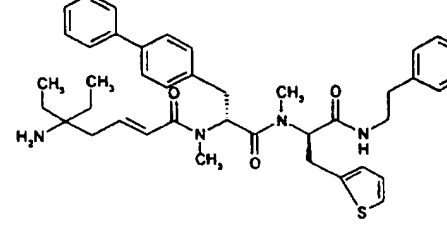
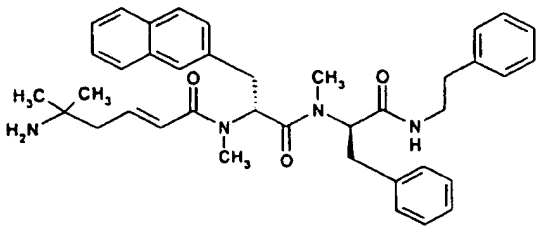
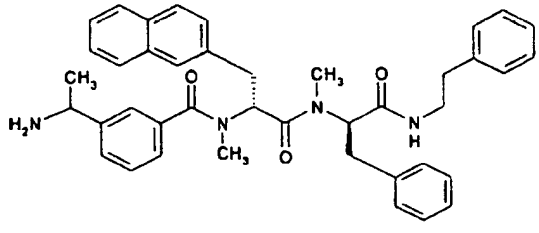
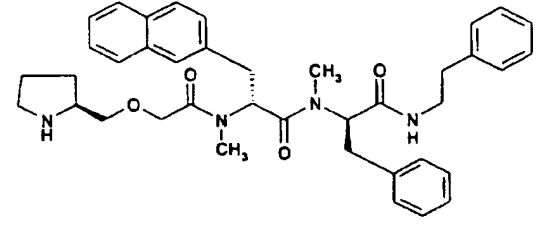
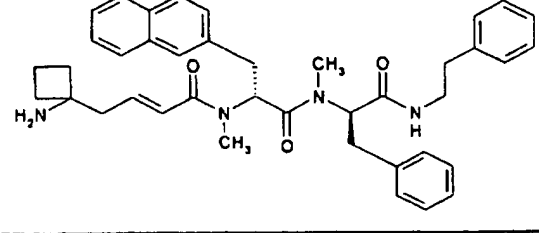
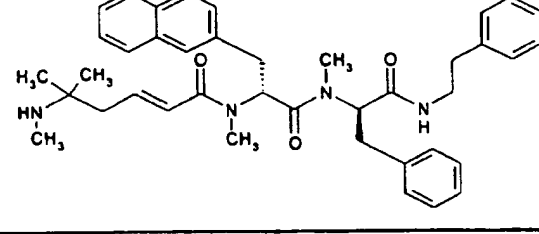
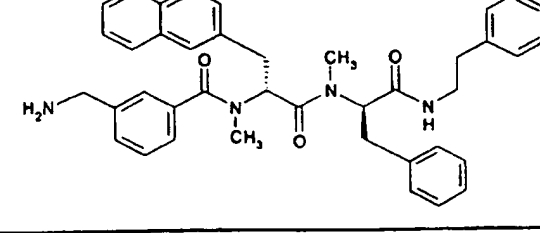
350		670,81		
351		678,83		
352		676,85		
353		690,88		

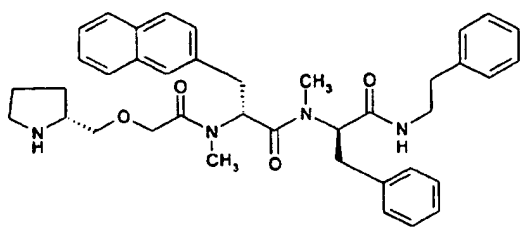
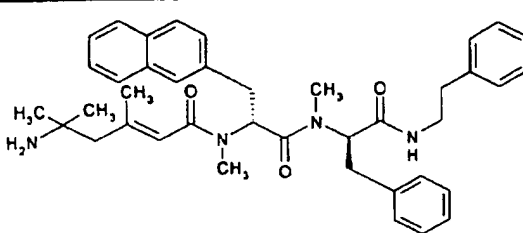
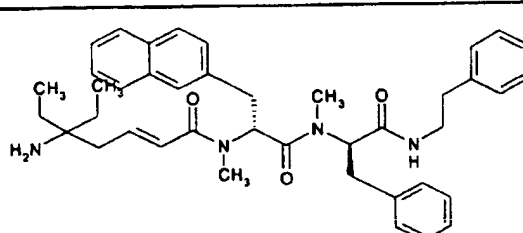
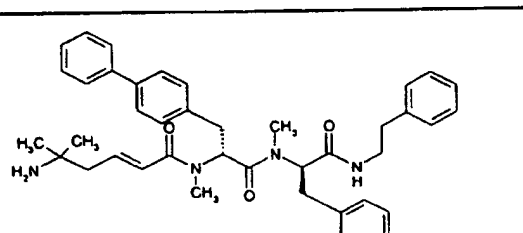
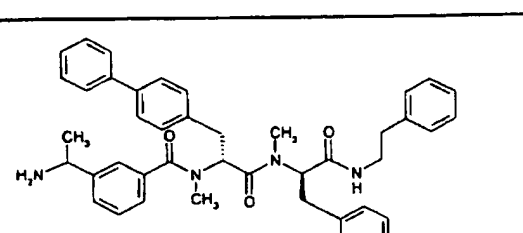
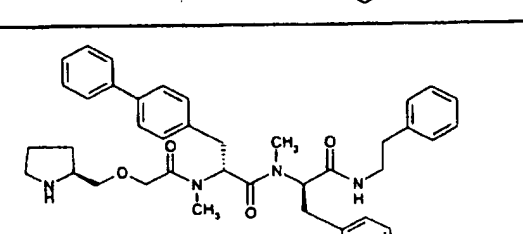
Table 3

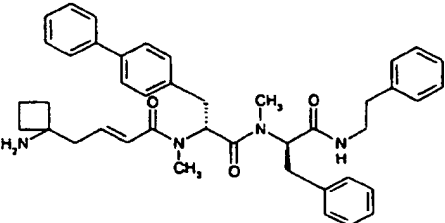
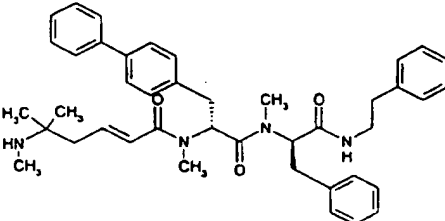
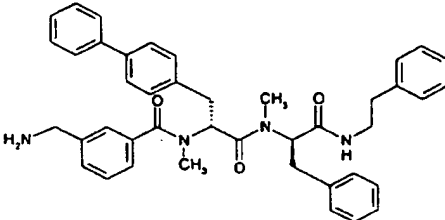
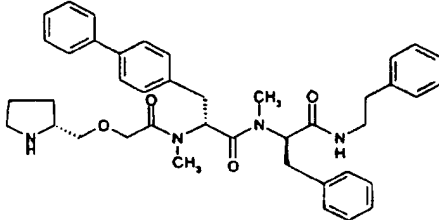
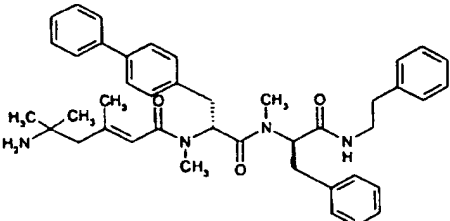
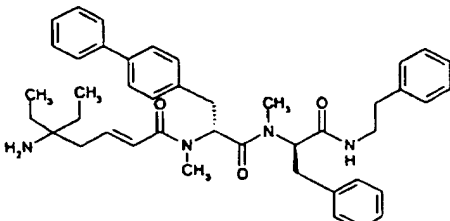
Example	Structure	MW	HPLC	LC-MS
354		624,9		
355		646,9		
356		640,9		
357		636,9		
358		638,9		
359		632,8		

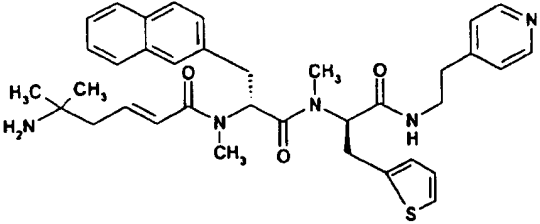
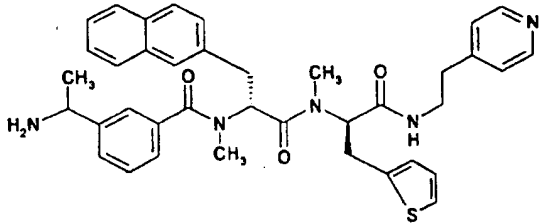
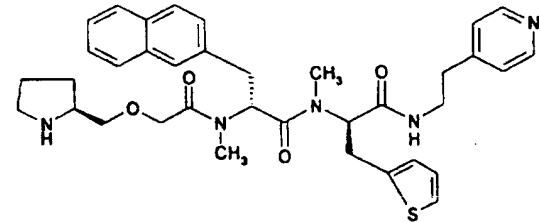
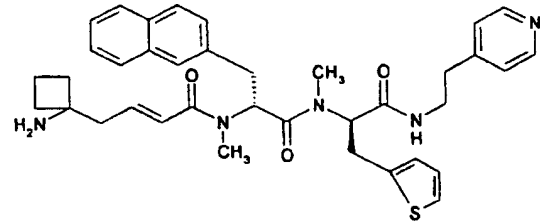
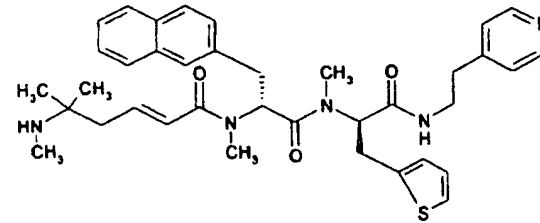
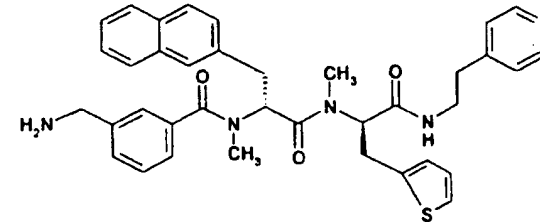
360		640,9		
361		638,9		
362		652,9		
363		650,9		
364		672,9		
365		666,9		

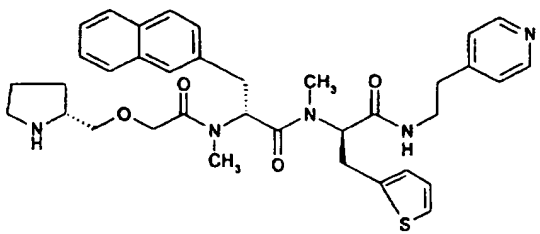
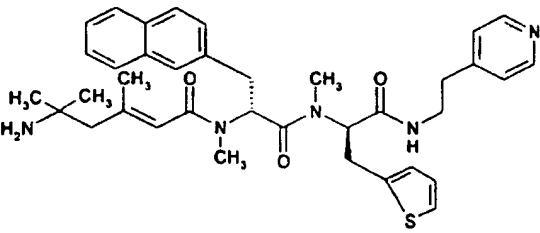
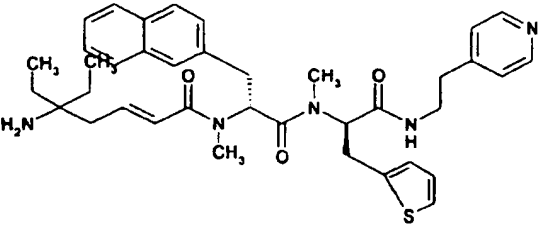
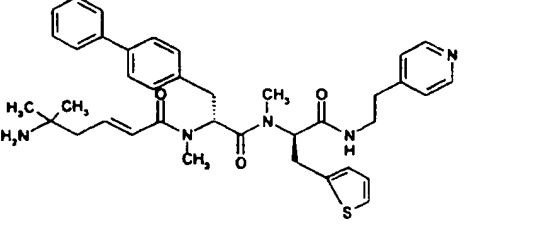
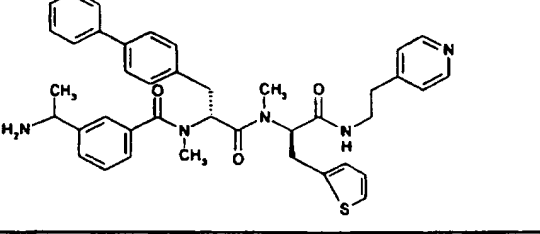
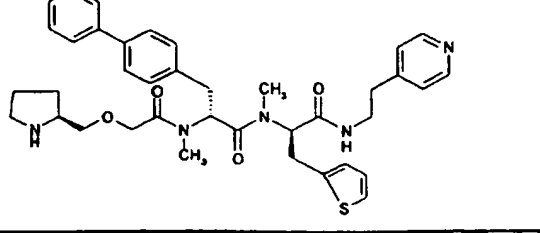
366		662,9		
367		664,9		
368		658,9		
369		666,9		
370		664,9		
371		678,9		

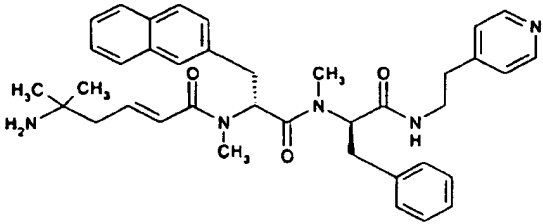
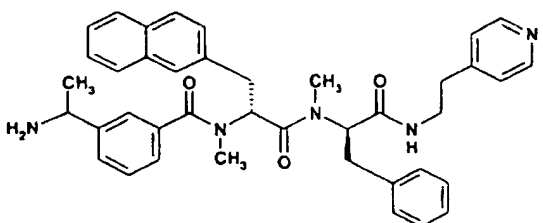
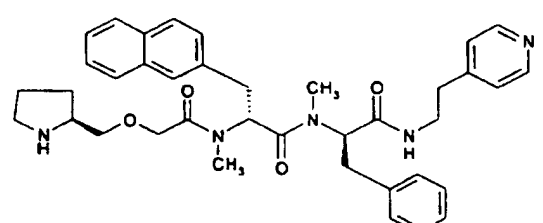
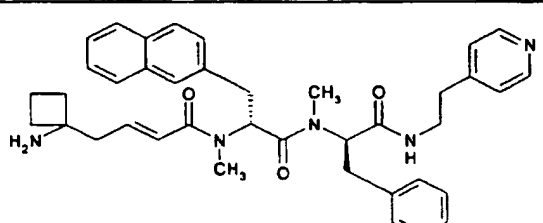
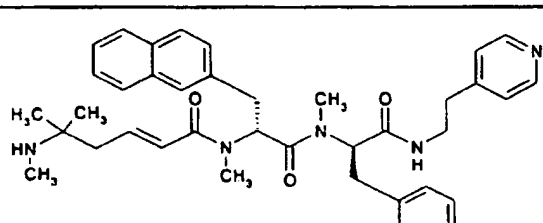
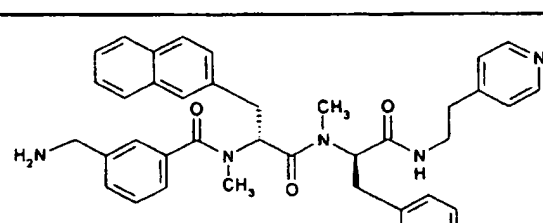
372		618,8		
373		640,8		
374		634,8		
375		630,8		
376		632,9		
377		626,8		

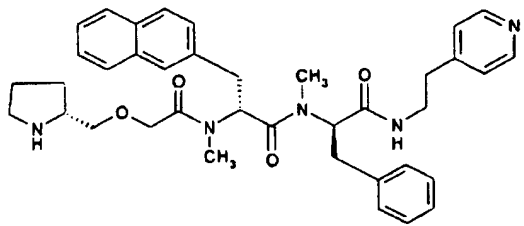
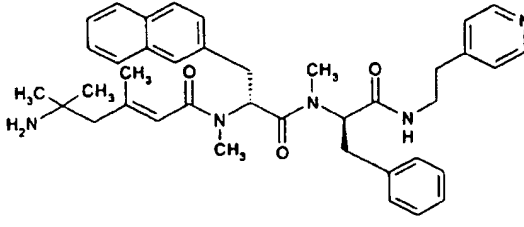
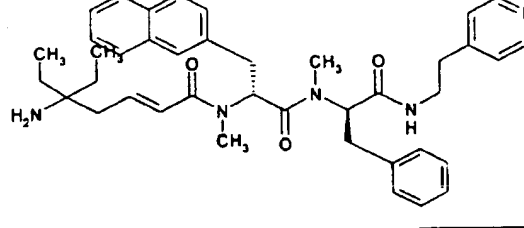
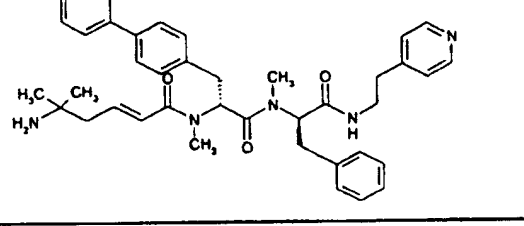
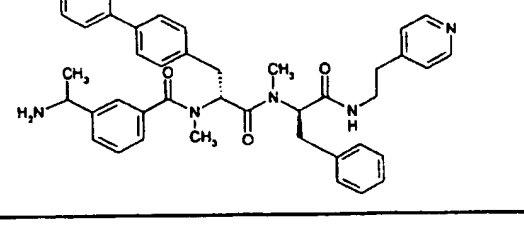
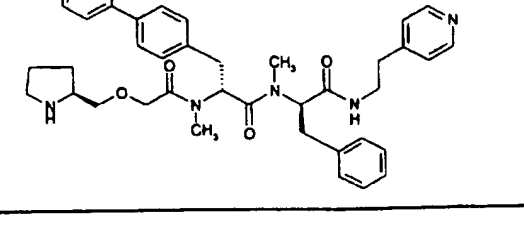
378		634,8		
379		632,9		
380		646,9		
381		644,9		
382		666,9		
383		660,9		

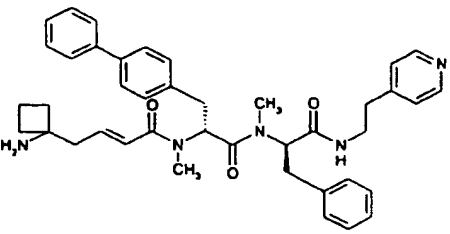
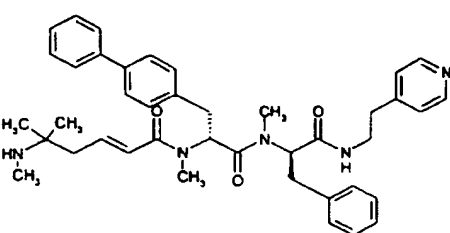
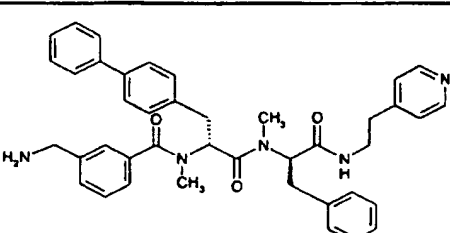
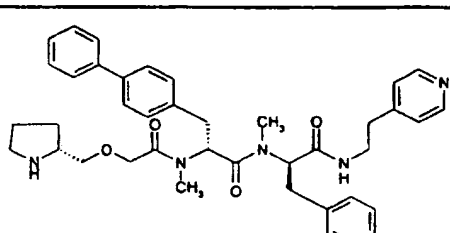
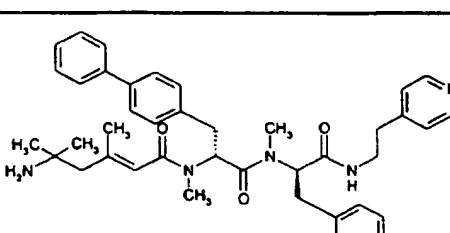
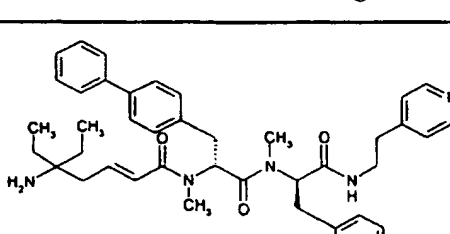
384		656,9		
385		658,9		
386		652,8		
387		660,9		
388		658,9		
389		672,9		

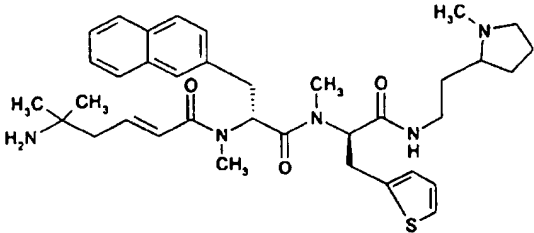
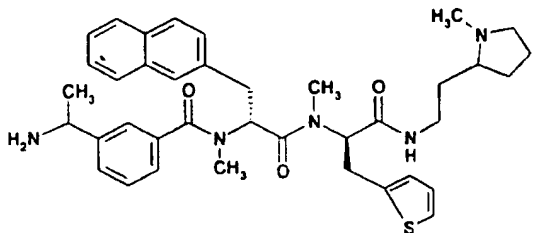
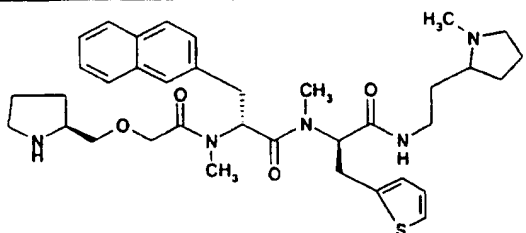
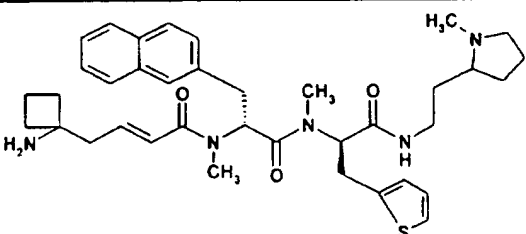
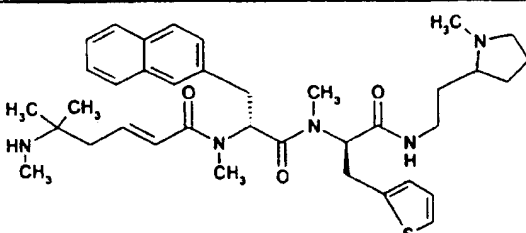
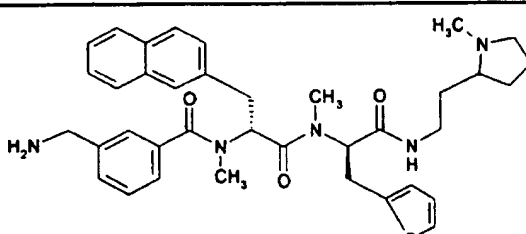
390		625,8		
391		647,8		
392		641,8		
393		637,9		
394		639,9		
395		633,8		

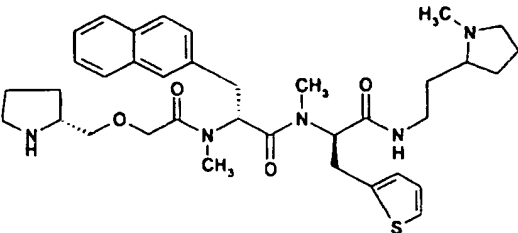
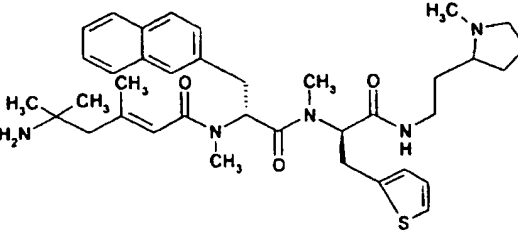
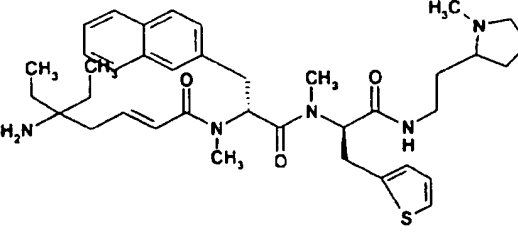
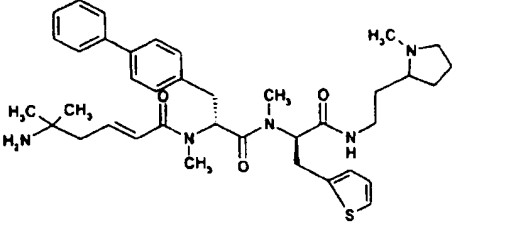
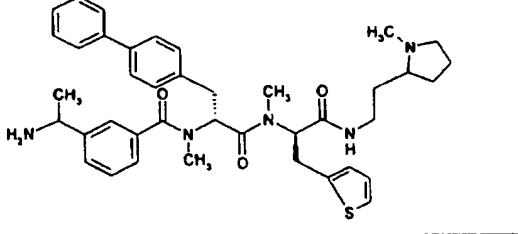
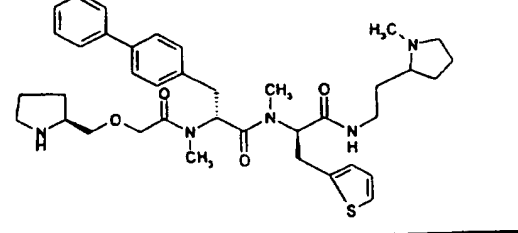
396		641,8		
397		639,9		
398		653,9		
399		651,9		
400		673,9		
401		667,9		

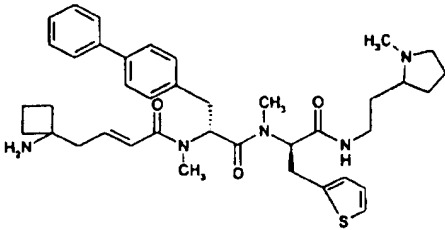
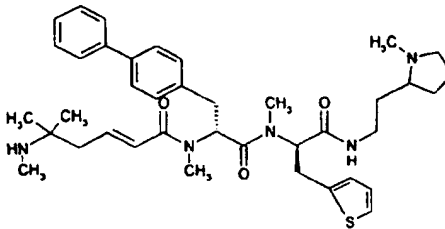
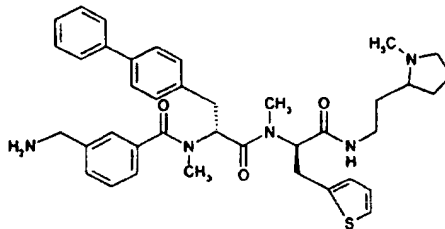
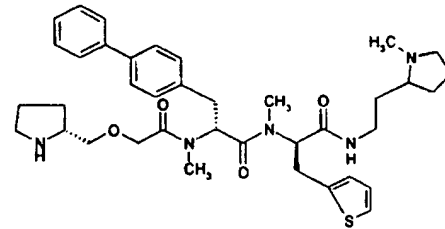
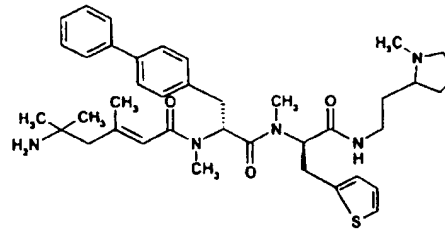
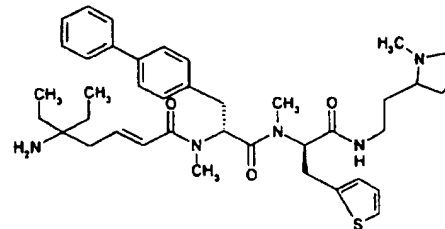
408		619,8		
409		641,8		
410		635,8		
411		631,8		
412		633,8		
413		627,8		

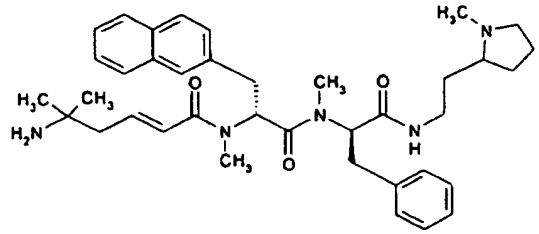
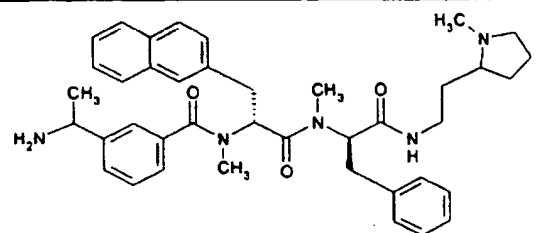
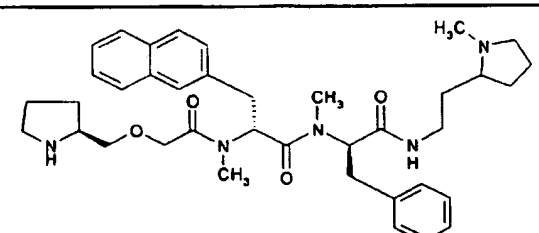
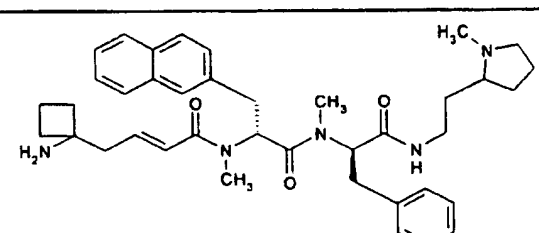
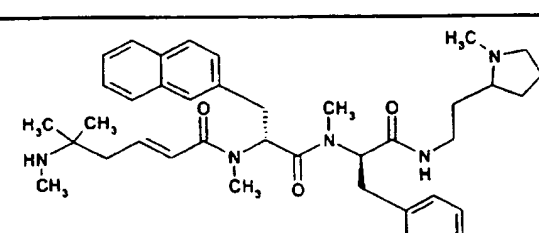
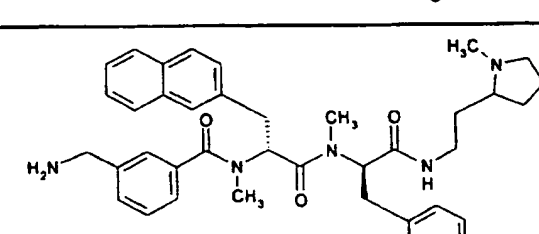
414		635,8		
415		633,8		
416		647,9		
417		645,9		
418		667,9		
419		661,9		

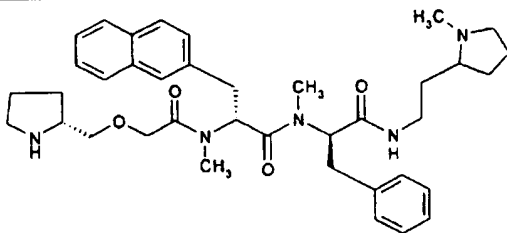
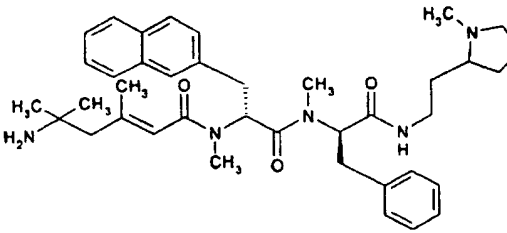
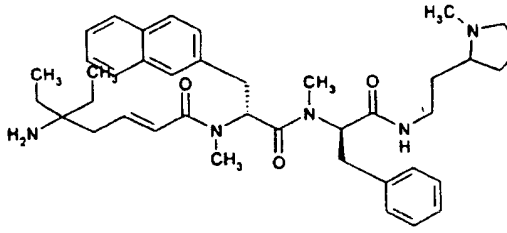
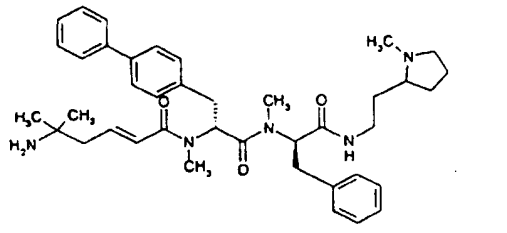
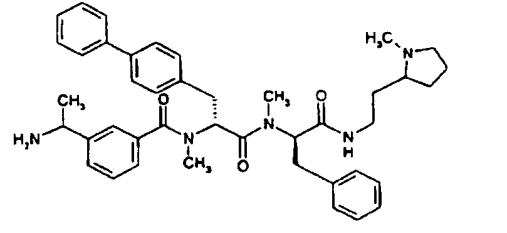
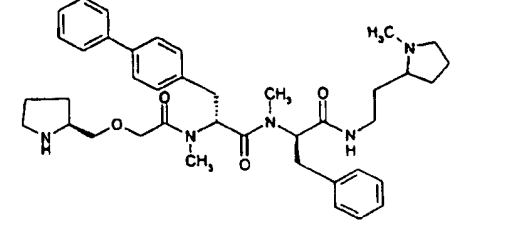
420		657,9		
421		659,9		
422		653,8		
423		661,9		
424		659,9		
425		673,9		

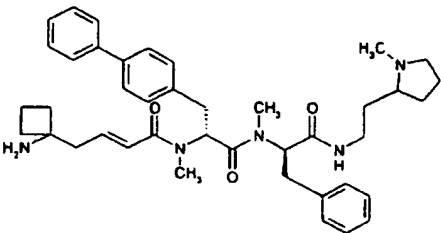
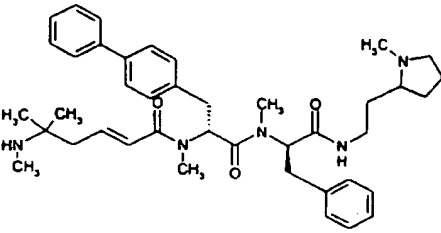
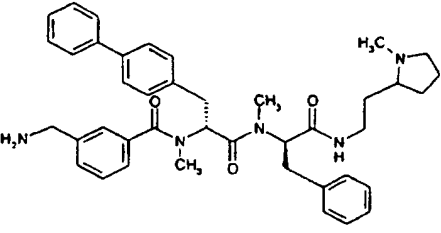
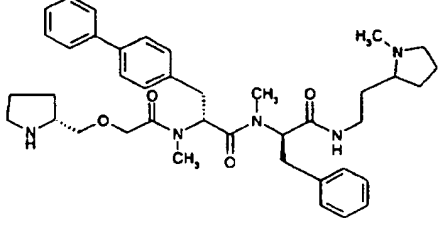
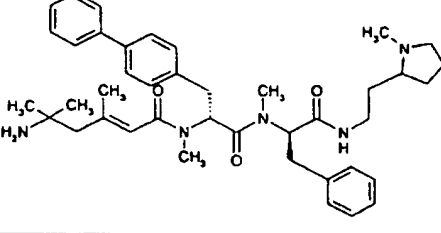
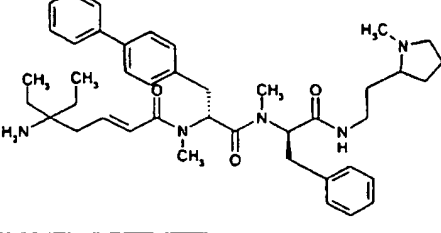
426		631,9		
427		653,9		
428		647,9		
429		643,9		
430		645,9		
431		639,9		

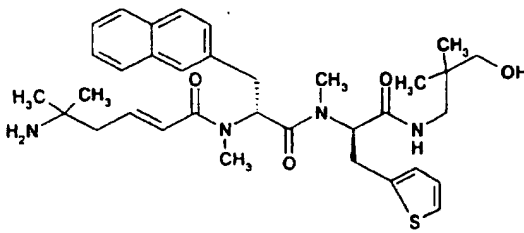
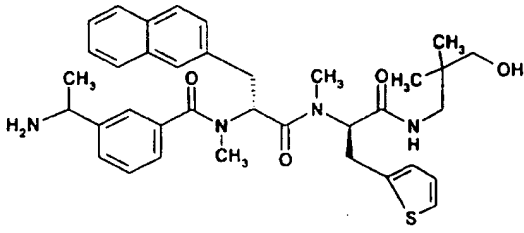
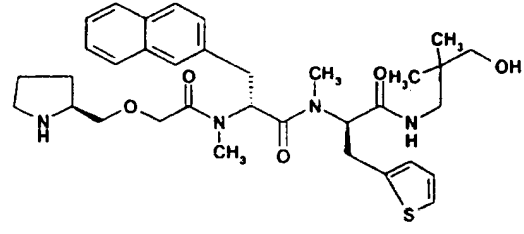
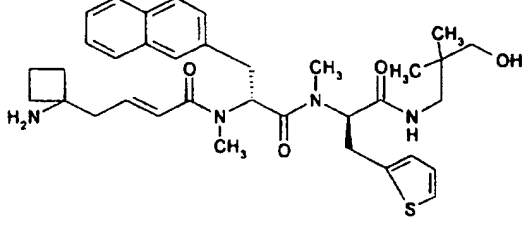
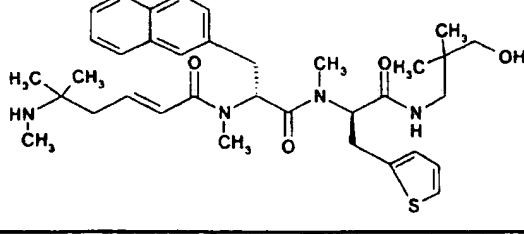
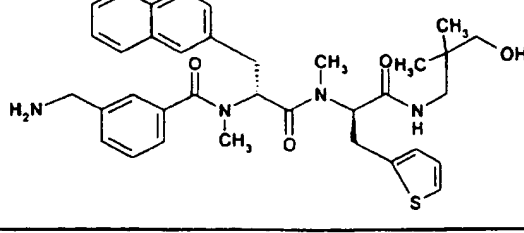
432		647,9		
433		645,9		
434		659,9		
435		657,9		
436		679,9		
437		673,9		

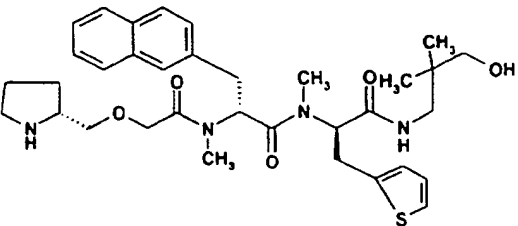
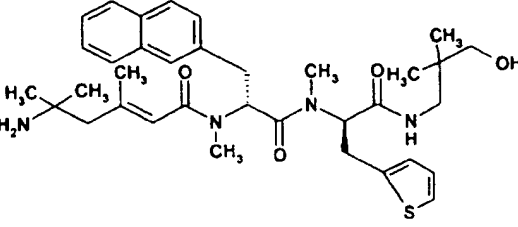
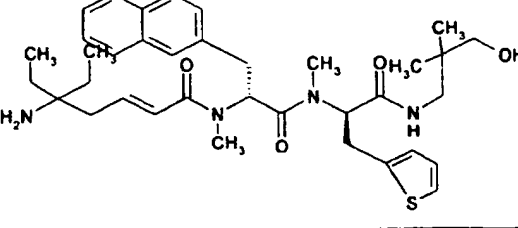
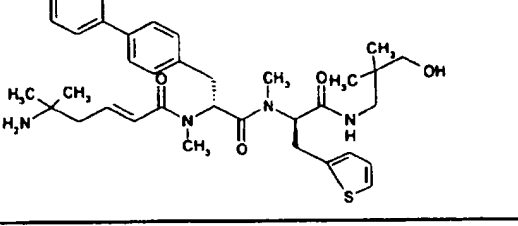
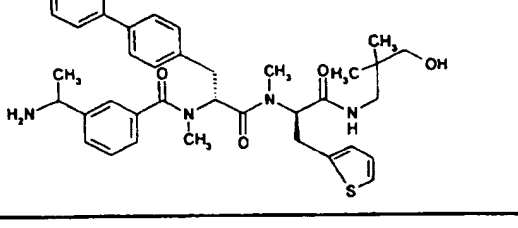
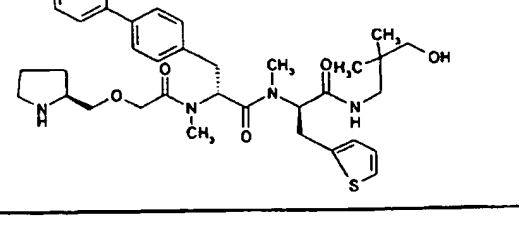
438		669,9		
439		672,0		
440		665,9		
441		673,9		
442		672,0		
443		686,0		

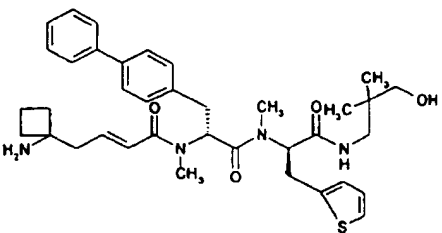
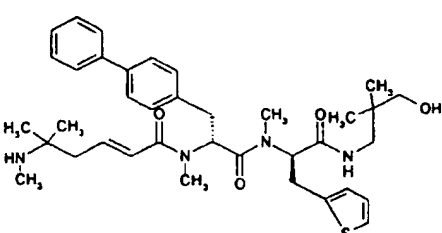
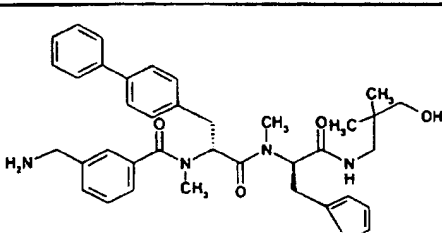
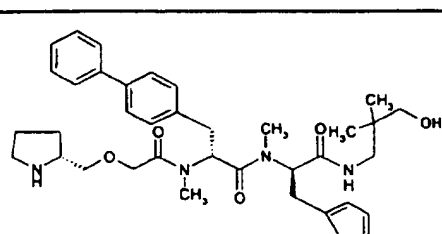
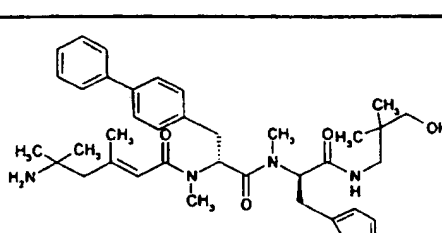
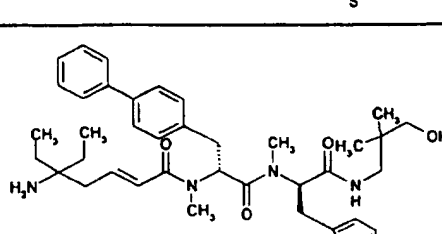
444		625,9		
445		647,9		
446		641,9		
447		637,9		
448		639,9		
449		633,8		

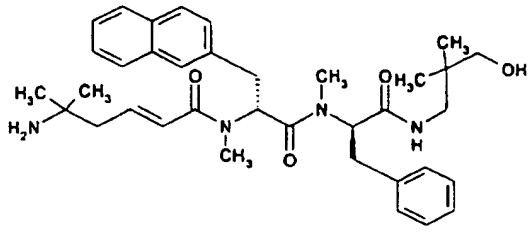
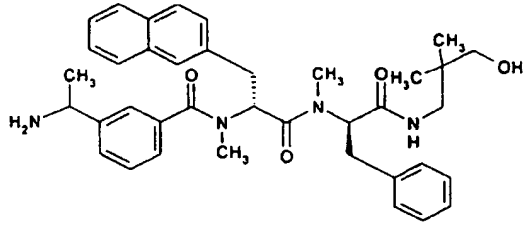
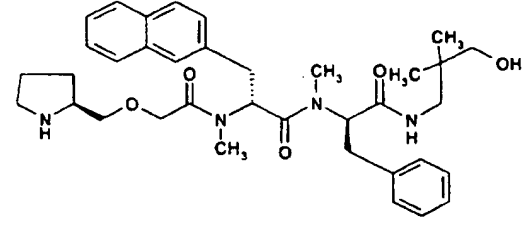
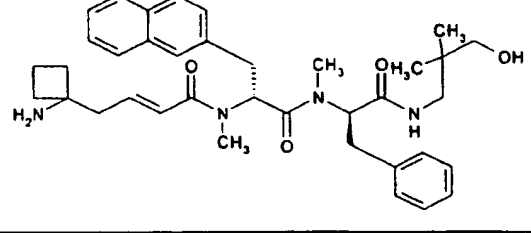
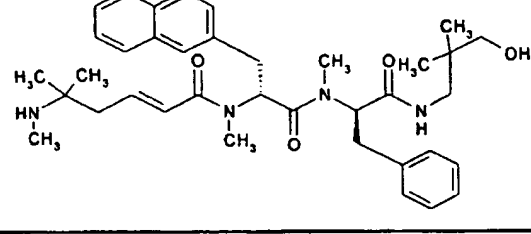
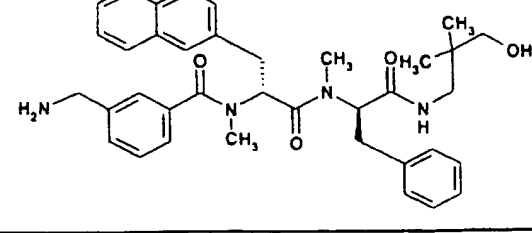
450		641,9		
451		639,9		
452		653,9		
453		651,9		
454		673,9		
455		667,9		

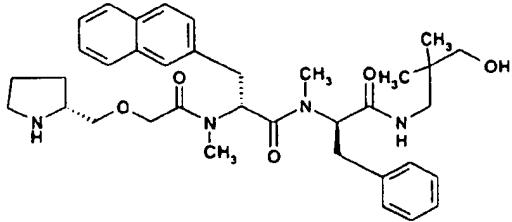
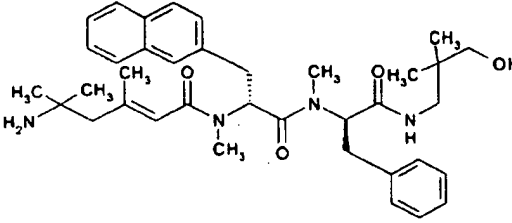
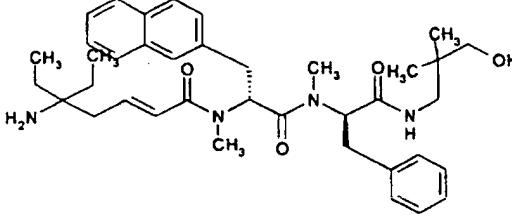
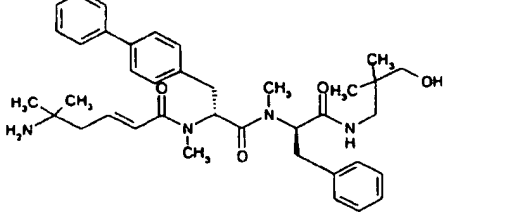
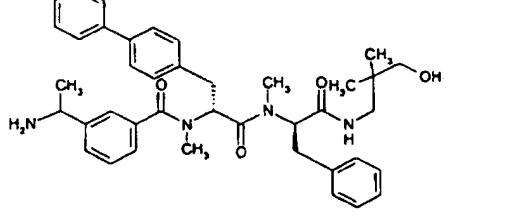
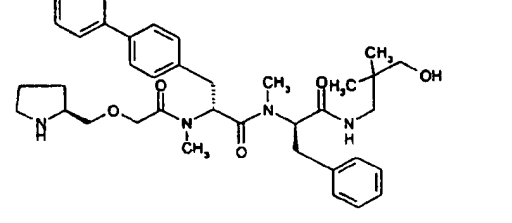
456		663,9		
457		665,9		
458		659,9		
459		667,9		
460		665,9		
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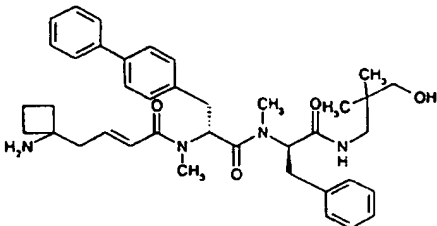
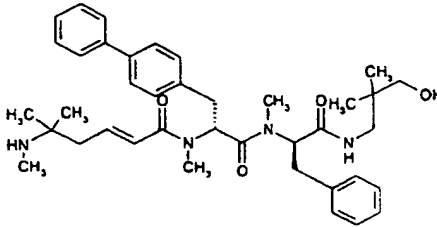
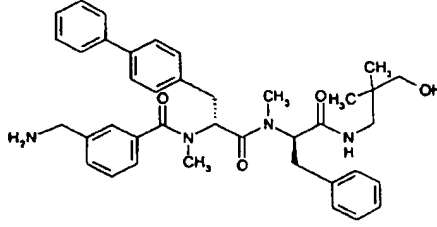
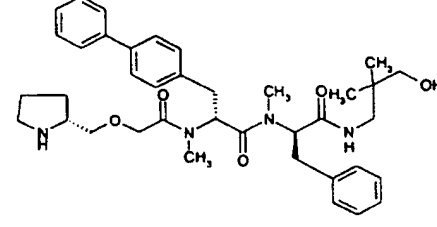
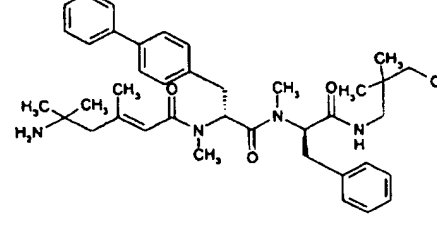
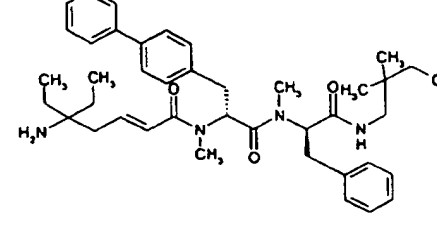
462		606,8		
463		628,8		
464		622,8		
465		618,8		
466		620,9		
467		614,8		

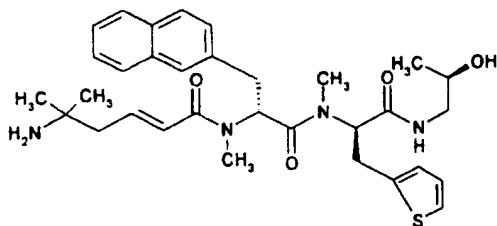
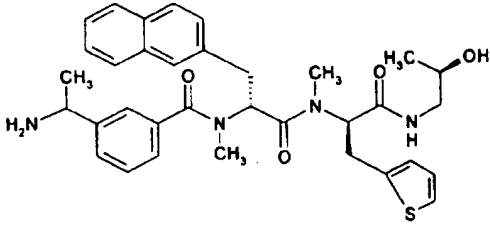
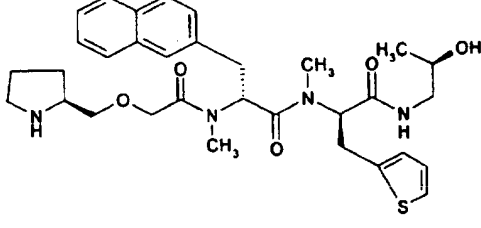
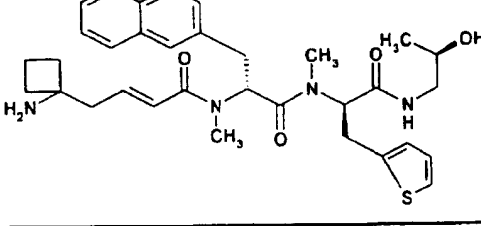
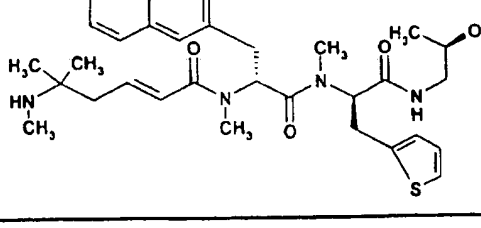
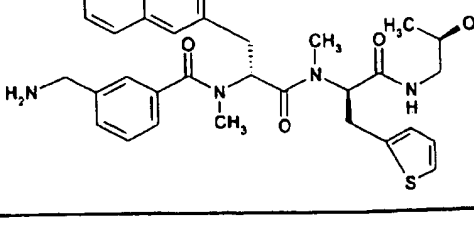
468		622,8		
469		620,9		
470		634,9		
471		632,9		
472		654,9		
473		648,9		

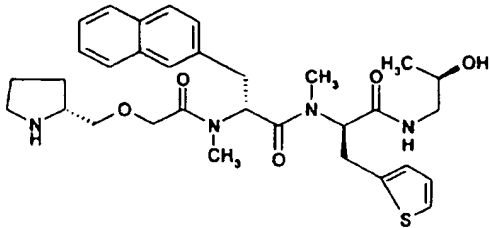
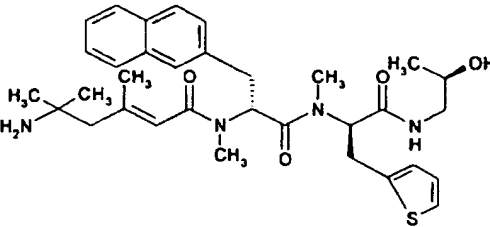
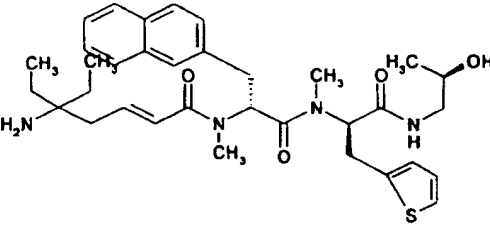
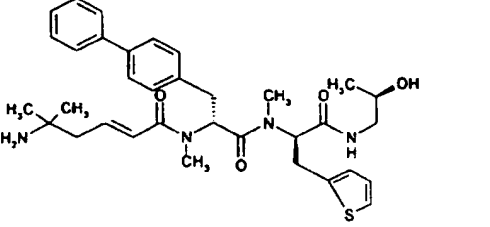
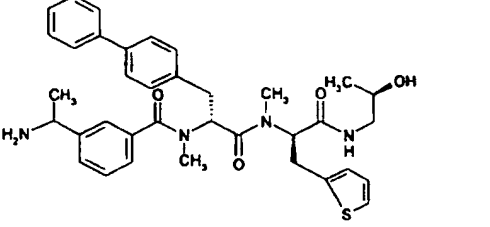
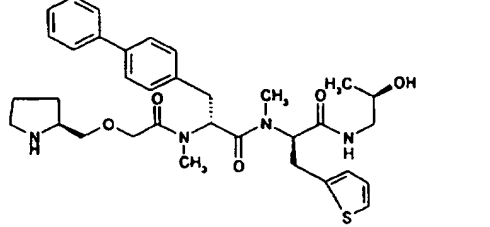
474		644,9		
475		646,9		
476		640,9		
477		648,9		
478		646,9		
479		660,9		

480		600,8		
481		622,8		
482		616,8		
483		612,8		
484		614,8		
485		608,8		

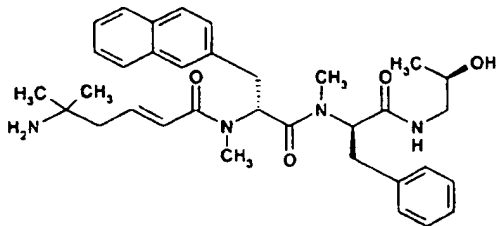
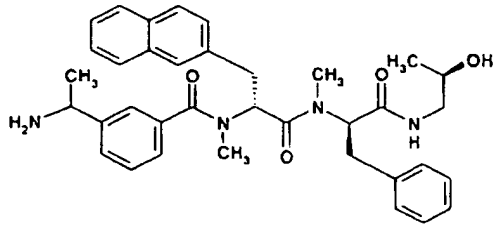
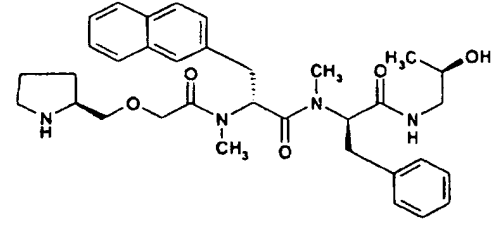
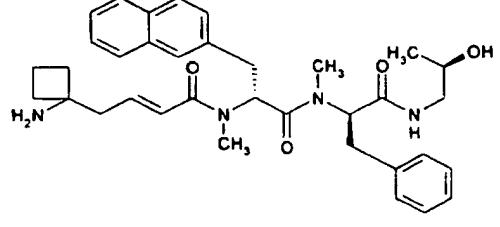
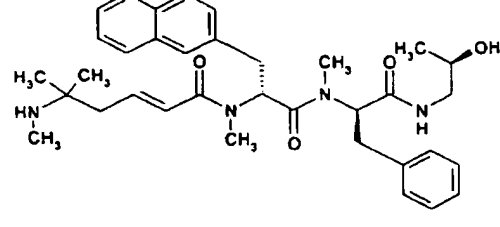
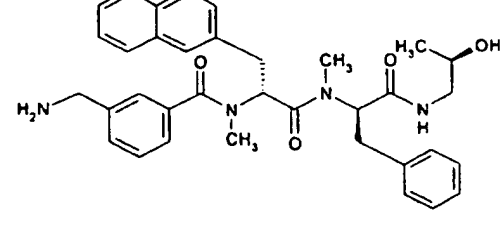
486		616,8		
487		614,8		
488		628,9		
489		626,8		
490		648,9		
491		642,8		

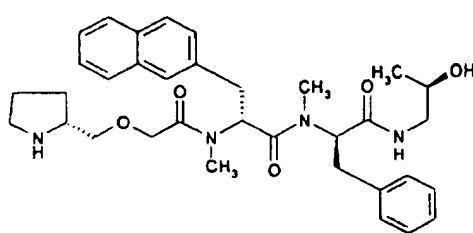
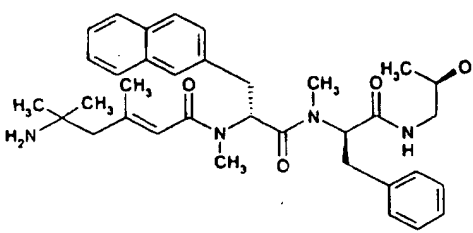
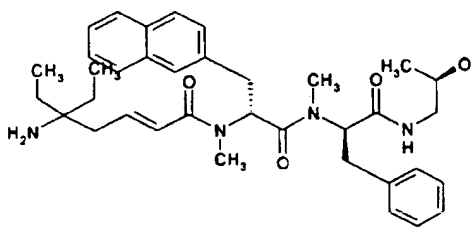
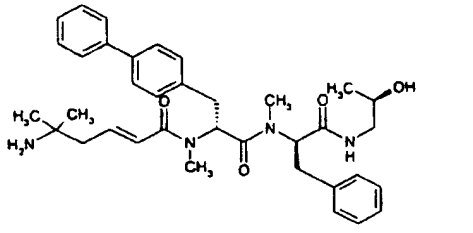
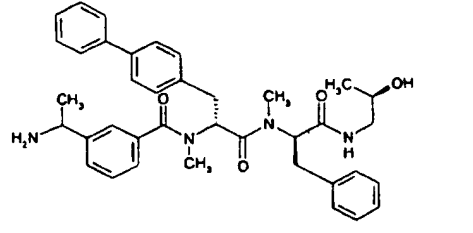
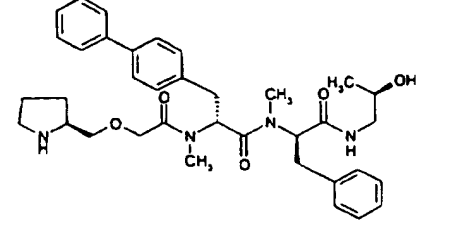
492		638,9		
493		640,9		
494		634,8		
495		642,8		
496		640,9		
497		654,9		

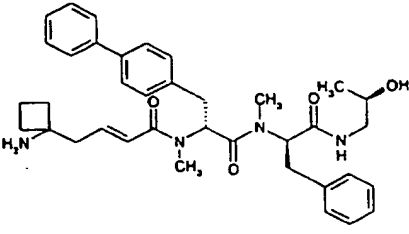
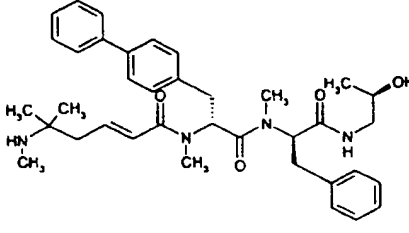
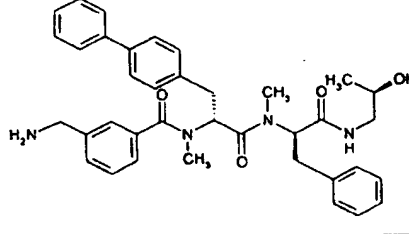
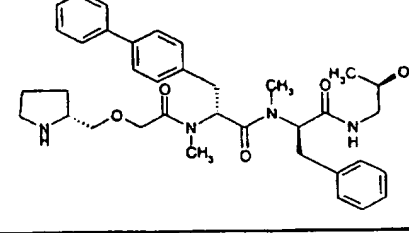
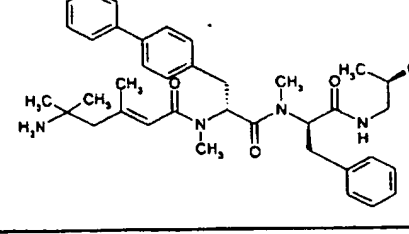
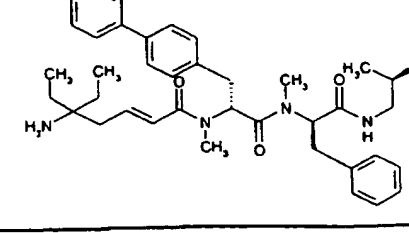
498		578,8		
499		600,8		
500		594,8		
501		590,8		
502		592,8		
503		586,8		

504		594,8		
505		592,8		
506		606,8		
507		604,8		
508		626,8		
509		620,8		

510		616,8		
511		618,8		
512		612,8		
513		620,8		
514		618,8		
515		632,9		

516		572,8		
517		594,8		
518		588,8		
519		584,8		
520		586,8		
521		580,7		

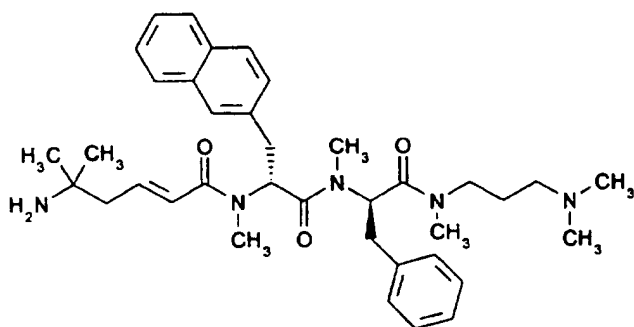
522		588,8		
523		586,8		
524		600,8		
525		598,8		
526		620,8		
527		614,8		

528		610,8		
529		612,8		
530		606,8		
531		614,8		
532		612,8		
533		626,8		

Example 534

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-1-(N-methyl-N-(3-dimethylaminopropyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

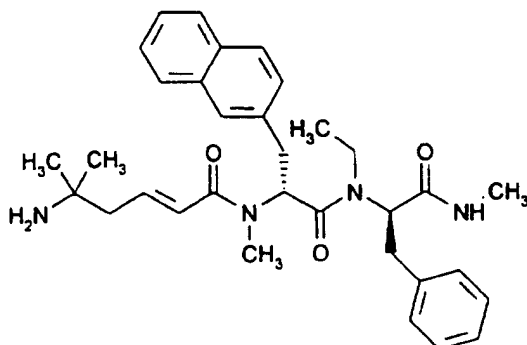


The title compound was prepared as in example 1 using N,N,N'-trimethylpropylenediamine instead of methylamine.

Example 535

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-1-(N-methylcarbamoyl)-2-phenylethyl)-N-ethylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide

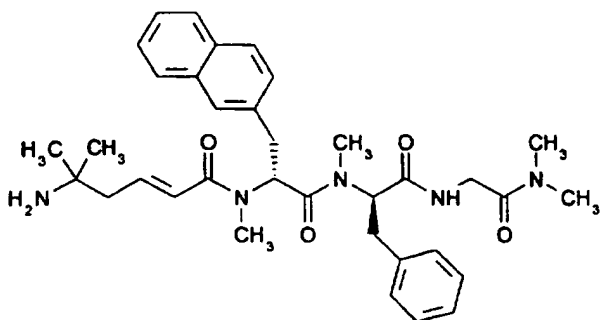


The title compound was prepared as in example 1. N-ethylation of D-Boc-phenylalanine was carried out by the use of ethyl iodide instead of methyl iodide.

5

Example 536

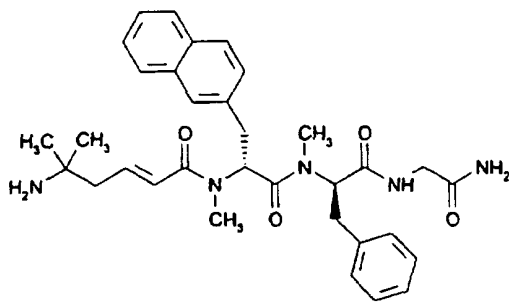
(2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-(N,N-
10 dimethylcarbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



The title compound was prepared as in example 1 using glycine dimethylamide
15 instead of methylamine.

Example 537

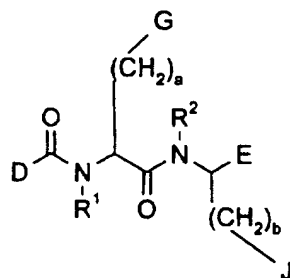
(2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-
20 (carbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide



The title compound was prepared as in example 1 using glycine amide instead of methylamine.

CLAIMS:

1. A compound of general formula I

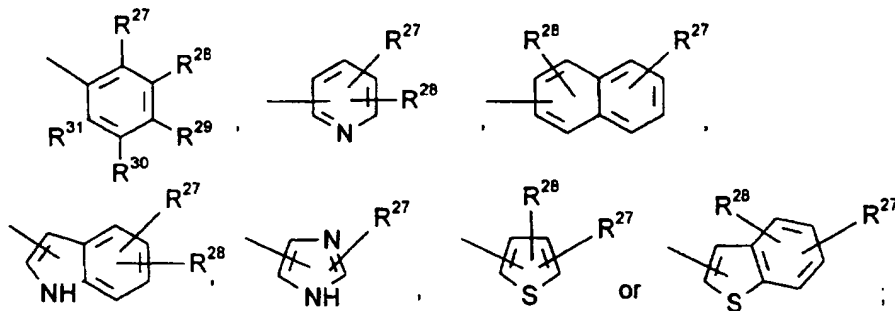


formula I

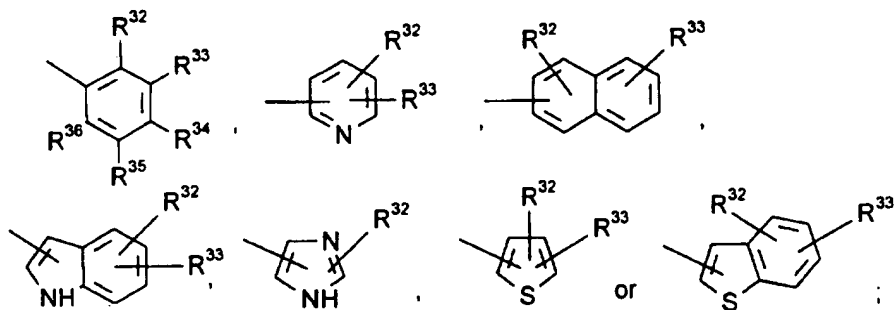
wherein

 R^1 and R^2 are independently hydrogen, or C_{1-6} -alkyl optionally substituted with aryl;

a and b are independently 1 or 2;

G is hydrogen, $-O-(CH_2)_k-R^{27}$,J is hydrogen, $-O-(CH_2)_l-R^{32}$,

461

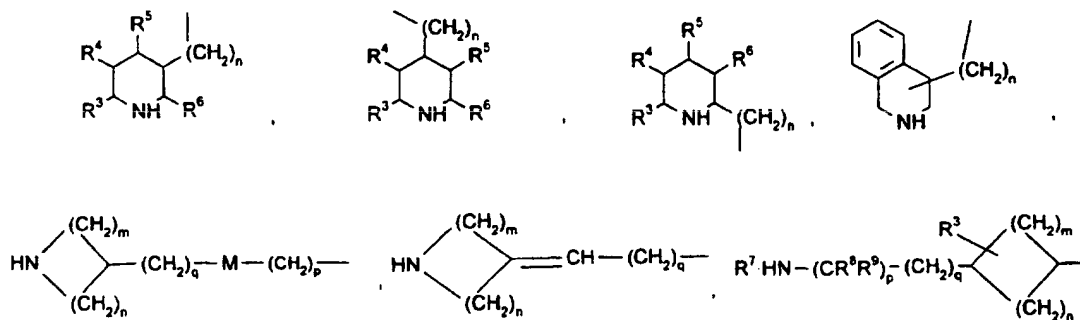


wherein R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} and R^{36} independently are hydrogen, halogen, aryl, C_{1-6} -alkyl or C_{1-6} -alkoxy;

k and l are independently 0, 1 or 2;

5

D is



10

15 wherein R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 are independently hydrogen or C_{1-6} -alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

n, m and q are independently 0, 1, 2, or 3;

p is 0 or 1;

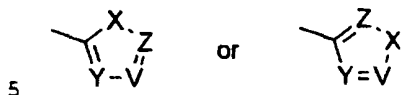
M is $-CR^{11}=CR^{11a}-$, aryl, $-O-$, or $-S-$;

20 R^{11} and R^{11a} are independently hydrogen, or C_{1-6} -alkyl optionally substituted with aryl;

with the proviso that at least one of R^3 , R^4 , R^5 and R^6 is different from hydrogen,

when E is

-CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},
 -(CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴,
 -(CH₂)_v-NR¹²-CO-NR¹³R¹⁴,



wherein

X is -N(R¹⁵)-, -O- or -S-,

V is -C(R¹⁶)= or -N=,

10 Y is -C(R¹⁷)= or -N=,

Z is -C(R¹⁸)= or -N=,

R¹⁵ is hydrogen or C₁₋₆-alkyl optionally substituted with aryl,

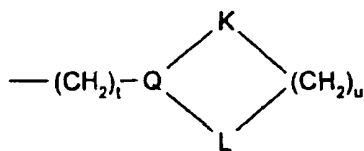
R¹⁶, R¹⁷ and R¹⁸ independently are hydrogen, -COOR¹⁹, -CONR²⁰R²¹, -

15 (CH₂)_wNR²⁰R²¹, -(CH₂)_wOR¹⁸, -(CH₂)_wR¹⁹ or halogen;

R¹², R¹³, R¹⁹, R²⁰ and R²¹ independently are hydrogen or C₁₋₆-alkyl optionally
 substituted with halogen, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl,
 C₁₋₆-alkylcarbonyloxy or aryl,

20

or R¹³ is



25 wherein

Q is -CH< or -N< ,

K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond,

where R²⁶ is hydrogen or C₁₋₆-alkyl;

t and u are independently 0, 1, 2, 3 or 4;

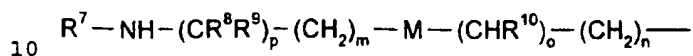
R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆-alkyl;

5 v and w are independently 0, 1, 2 or 3; or

D is



wherein R⁷, R⁸, R⁹ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl optionally substituted with halogen, amino, hydroxyl or aryl;

R⁷ and R⁸ or R⁷ and R⁹ or R⁸ and R⁹ optionally forming -(CH₂)_i-U-(CH₂)_j-, wherein i

15 and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

n and m are independently 0, 1, 2, or 3;

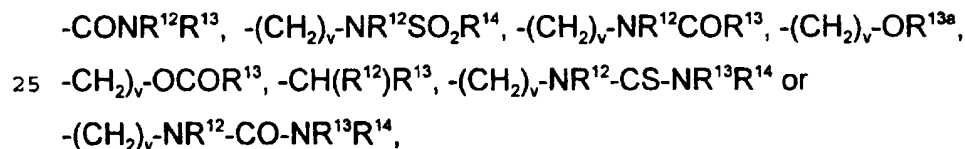
o and p are independently 0 or 1;

M is -CR¹¹=CR^{11a}-, aryl, -O-, or -S-;

R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with

20 aryl,

when E is

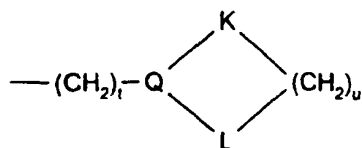


wherein

R¹² and R¹³ independently are hydrogen or C₁₋₆-alkyl optionally substituted with

30 halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkylcarbonyloxy or aryl;

or R^{13} is



wherein

5 Q is $-\text{CH}<$ or $-\text{N}<$,

K and L are independently $-\text{CH}_2-$, $-\text{CO}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{26}-$ or a valence bond,

where R^{26} is hydrogen or C_{1-6} alkyl;

t and u are independently 0, 1, 2, 3 or 4;

R^{13a} is C_{1-6} alkyl substituted with aryl;

10 R^{14} is C_{1-6} alkyl;

R^{22} and R^{23} are independently hydrogen or C_{1-6} alkyl;

v and w are independently 0, 1, 2 or 3;

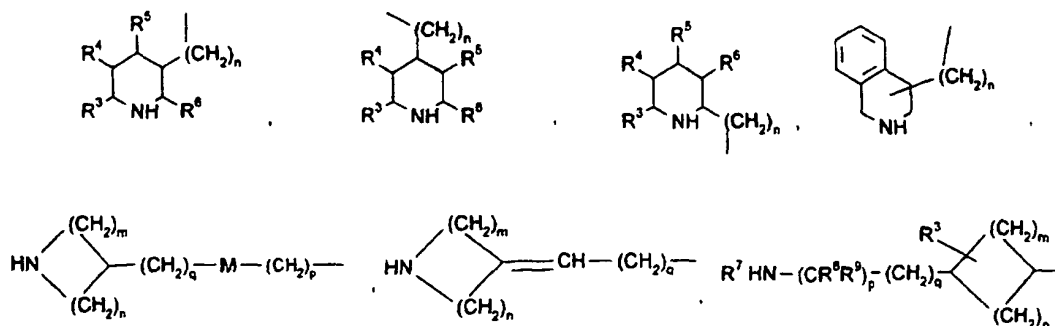
or a pharmaceutically acceptable salt thereof.

15

2. The compound according to claim 1 wherein

D is

20



wherein R^3 , R^4 , R^5 , R^6 , R^8 and R^9 are independently hydrogen or methyl;

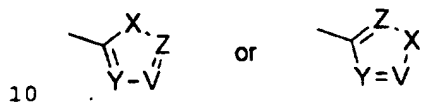
n, m and q are independently 0, 1 or 2;

M is $-\text{CR}^{11}=\text{CR}^{11a}-$, aryl or $-\text{O}-$;

R^{11} and R^{11a} are independently hydrogen, or C_{1-6} -alkyl optionally substituted with aryl,

- 5 with the proviso that at least one of R^3 , R^4 , R^5 and R^6 is different from hydrogen, when E is

$-\text{CONR}^{12}\text{R}^{13}$, $-(\text{CH}_2)_v-\text{NR}^{12}\text{SO}_2\text{R}^{14}$, $-(\text{CH}_2)_v-\text{NR}^{12}\text{COR}^{13}$, $-(\text{CH}_2)_v-\text{OR}^{13a}$,
 $-(\text{CH}_2)_v-\text{OCOR}^{13}$, $-\text{CH}(\text{R}^{12})\text{R}^{13}$, $-(\text{CH}_2)_v-\text{NR}^{12}-\text{CS}-\text{NR}^{13}\text{R}^{14}$,
 $-(\text{CH}_2)_v-\text{NR}^{12}-\text{CO}-\text{NR}^{13}\text{R}^{14}$,



X is $-\text{N}(\text{R}^{15})-$, $-\text{O}-$ or $-\text{S}-$,

V is $-\text{C}(\text{R}^{16})=$ or $-\text{N}=$,

Y is $-\text{C}(\text{R}^{17})=$ or $-\text{N}=$,

Z is $-\text{C}(\text{R}^{18})=$ or $-\text{N}=$,

15

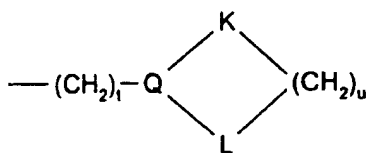
R^{15} is hydrogen or C_{1-6} -alkyl optionally substituted with aryl,

R^{16} , R^{17} and R^{18} independently are hydrogen, $-\text{COOR}^{19}$, $-\text{CONR}^{20}\text{R}^{21}$, $-(\text{CH}_2)_w\text{NR}^{20}\text{R}^{21}$, $-(\text{CH}_2)_w\text{OR}^{19}$, $-(\text{CH}_2)_w\text{R}^{19}$ or halogen;

- 20 R^{12} , R^{13} , R^{19} , R^{20} and R^{21} independently are hydrogen or C_{1-6} -alkyl optionally substituted with halogen, $-\text{N}(\text{R}^{22})\text{R}^{23}$, $-\text{CF}_3$, hydroxyl, C_{1-6} -alkoxy, C_{1-6} -alkoxycarbonyl, C_{1-6} -alkylcarbonyloxy or aryl,

or R^{13} is

25



wherein

Q is -CH< or -N< ,

K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond,
where R²⁶ is hydrogen or C₁₋₆-alkyl;

t and u are independently 0, 1, 2, 3 or 4;

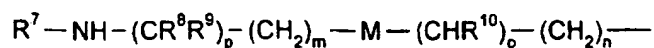
5 R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆-alkyl; and

v and w are independently 0, 1, 2 or 3.

10 3. A compound according to claim 1 wherein D is



wherein R⁸ and R⁹ are independently hydrogen or methyl;

15 R⁷ and R¹⁰ are independently hydrogen or C₁₋₆ alkyl optionally substituted by
halogen, amino, hydroxyl or aryl;

or R⁷ and R⁸ or R⁸ and R⁹ can form -(CH₂)_i-U-(CH₂)_j-, wherein i and j independently
are 1 or 2 and U is -O-, -S- or a valence bond;

n and m are independently 0, 1, or 2;

20 M is -CR¹¹=CR^{11a}-, aryl or -O-;

R¹¹ and R^{11a} are independently hydrogen, or C₁₋₆-alkyl optionally substituted with
aryl,

when E is

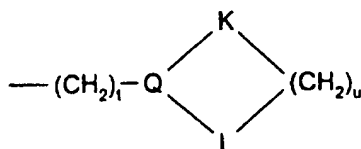
25 -CONR¹²R¹³, -(CH₂)_v-NR¹²SO₂R¹⁴, -(CH₂)_v-NR¹²COR¹³, -(CH₂)_v-OR^{13a},
-(CH₂)_v-OCOR¹³, -CH(R¹²)R¹³, -(CH₂)_v-NR¹²-CS-NR¹³R¹⁴ or
-(CH₂)_v-NR¹²-CO-NR¹³R¹⁴,

30 wherein

R¹² and R¹³ independently are hydrogen or C₁₋₆-alkyl optionally substituted with
halogen, -CONR²²R²³, -N(R²²)R²³, -CF₃, hydroxyl, C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl,

C₁₋₆-alkylcarbonyloxy or aryl;

or R¹³ is



5

wherein

Q is -CH< or -N< ,

K and L are independently -CH₂-, -CO-, -O-, -S-, -NR²⁶- or a valence bond,
where R²⁶ is hydrogen or C₁₋₆ alkyl;

10 t and u are independently 0, 1, 2, 3 or 4;

R^{13a} is C₁₋₆ alkyl substituted with aryl;

R¹⁴ is C₁₋₆ alkyl;

R²² and R²³ are independently hydrogen or C₁₋₆ alkyl;

v and w are independently 0, 1, 2 or 3.

15

4. A compound according to claim 1, 2 or 3 wherein D is

3-(1-aminoethyl)phenyl, 4-amino-4-ethylhex-1-enyl, (1E)-2-(azetidin-3-yl)ethenyl,
piperidin-4-ylidenyl, 2-methylpiperidin-4-yl, 2-methylpiperidin-3-yl, 2-
methylpiperidin-5-yl, (1,2,3,4-tetrahydroisoquinolin-1-yl)methyl, 4-

20 aminocyclohexyl, 2-piperidylmethoxymethyl, 4-piperidyloxymethyl,

2-(2-amino-2-methylpropyl)cyclopropyl, (((2R)-pyrrolidin-2-yl)methoxy)methyl,

(1E)-4-amino-1-benzyl-4-methylpent-1-enyl, (1E)-4-amino-4-methylpent-1-enyl,

(2-amino-2-methylpropoxy)methyl, (2S)-(2-pyrrolidinyl)methoxymethyl, (2R)-(2-

pyrrolidinyl)methoxymethyl, (1E)-4-amino-2,4-dimethylpent-1-enyl, (1E)-4-methyl-

25 4-(methylamino)pent-1-enyl, (1Z)-4-amino-4-methylpent-1-enyl,

(1E)-4-((2R)-2-hydroxypropylamino)-4-methylpent-1-enyl,

(2-aminobutoxy)methyl, 3-(1-aminoethyl)phenyl, 3-aminomethylphenyl, 3-(1-

amino-1-methylethyl)phenyl, 2-(1-aminocyclopropyl)ethenyl, 3-(1-

aminocyclobutyl)-1-propenyl, 3-(1-aminocyclopropyl)-1-propenyl or 2-(1-amino

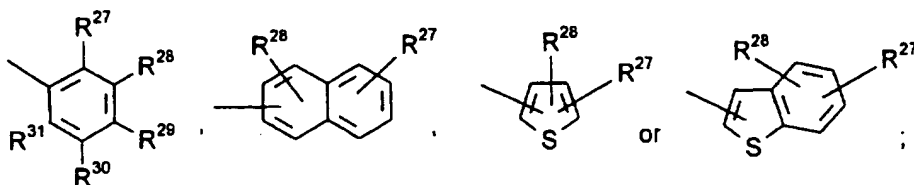
cyclobutyl)ethenyl.

5. A compound according to claim 1, 2 or 3 wherein E is methylcarbamoyl, ethylcarbamoyl, N,N-dimethylcarbamoyl, 2-methoxyethylcarbamoyl, (2S)-2-hydroxypropylcarbamoyl, (2R)-2-hydroxypropylcarbamoyl, (cyclopropylmethyl)carbamoyl, (2-(acetoxy)-2-methylpropyl)carbamoyl, phenylethylcarbamoyl, 4-pyridylcarbamoyl, (3-acetoxypropyl)carbamoyl, (3-hydroxypropyl)carbamoyl, methylsulfonylaminomethyl, ((tetrahydrofuran-2-yl)methyl)carbamoyl, 3-cyclopropylthioureido, N-methyl-N-(methylsulfonylamino)methyl, (2,2,2-trifluoroethyl)carbamoyl, cyclopropylcarbamoyl, ((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl, 3-methyl-1,2,4-oxadiazol-5-yl, methylsulfonylaminomethyl, 2,2-dimethyl-3-hydroxypropylcarbamoyl, 2-(1-methylpyrrolidine-2-yl)ethylcarbamoyl, N-methyl-N-(3-(dimethylamino)propyl)carbamoyl, N-(N,N-dimethylcarbamoyl)-N-methylcarbamoyl, N-(carbamoylmethyl)carbamoyl or 3-cyclopropylthioureido.

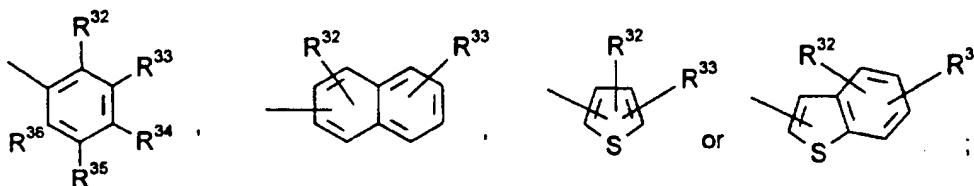
6. The compound according to any one of claims 1-5 wherein R¹ and R² independently are hydrogen, methyl or ethyl.

7. The compound according to any one of the claims 1-6 wherein a and b independently are 1.

8. A compound according to any one of the claims 1-7 wherein G is hydrogen, -O-(CH₂)_k-R²⁷,



J is hydrogen, -O-(CH₂)_l-R³²



wherein R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} and R^{36} independently are hydrogen, halogen, aryl, C_{1-6} -alkyl or C_{1-6} -alkoxy; and k and l are 1.

5

9. A compound according to any one of the claims 1-8 wherein R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} and R^{36} are hydrogen, halogen, or phenyl.

10. A compound according to claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 selected from the group consisting of

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, or the hydrochloride salt,

15

(2E)-3-(3-Azetidinyl)acrylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-(Piperidin-4-ylidene)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

20

2-(2-Amino-2-methylpropyl)cyclopropanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

25

2-(2-Amino-2-methylpropoxy)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-Methylpiperidine-4-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

30

- 2-Methylpiperidine-3-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,
- 5 2-Methylpiperidine-5-carboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,
- 2-(1,2,3,4-Tetrahydroisoquinolin-1-yl)acetic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,
- 10 4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,
- (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(benzylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,
- 15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(phenethylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,
- (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-(acetylaminomethyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylamide,
- 20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-methyl-N-[(1R)-1-(methylsulfonylaminomethyl)-2-phenylethyl]carbamoyl}-2-(2-naphthyl)ethyl)amide,
- 25 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-((cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,
- 30 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-(2-methoxyethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((N-tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

5 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(N-2-hydroxypropylcarbamoyl)-2-phenylethyl)N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
10 (N-(3-(2-oxopyrrolidin-1-yl)propyl)carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-{N-[(1R)-1-((2,5-dioxopyrrolidine-1-yl)methyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-
15 naphthyl)ethyl)-N-methylamide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-N-methyl-3-(2-naphthyl)-N-((1R)-2-phenyl-1-((tetrahydrofuran-2-yl)methyl)carbamoyl)-ethyl)propionamide,

20

(2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((2-tetrahydrofuranyl)methyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-benzyloxy-1-(N-methyl-N-((1R)-
25 1-methylcarbamoyl-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-1-(cyclopropylmethyl)carbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)-propionamide,

30

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)methylamino)-N-((1R)-2-(2-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-3-(2-naphthyl)propionamide,

(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

10 (2E)-5-Amino-3,5-dimethylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

2-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)-1,1-dimethylethyl
15 acetate,

(2E)-5-Amino-2-benzyl-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

20 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-carbamoyl)-2-(1-naphthyl)ethyl)amide,

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)-3-(1-naphthyl)propionamide,

25

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-(benzo[b]thiophen-3-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methyl-amino)-3-(benzo-[b]thiophen-3-yl)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-propionamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-(((tetrahydrofuran-2-yl)-methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide,

5

3-((2R)-2-(N-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate, or the hydrochloride salt,

- 10 (2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(3-hydroxypropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide, or the acetate salt,

- 15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)methyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, or the hydrochloride salt,

N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[[2-(piperidinyl)methoxy]acetyl]amino)-3-(2-naphthyl)propionamide,

20

4-Aminocyclohexanecarboxylic acid N-methyl-N-((1R)-1-[N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl]-2-(2-naphthyl)ethyl)amide, or the acetate salt,

- 25 (2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[[piperidin-4-yloxy]acetyl]amino)-3-(2-naphthyl)propionamide,

2- Methyl-piperidine-4-carboxylic acid

N-{1-[N-methyl-N-(1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-(2-naphthyl)ethyl)carbamoyl]-

- 30 2-(2-naphthyl)ethyl} amide, or the acetate salt;

(2R)-2-(N-((2R)-2-(N-((2E)-5-((2R)-2-Hydroxypropylamino)-5-methylhex-2-enoyl)-N-

methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-N-methyl-3-phenylpropionamide;

(2E)-5-Amino-N-((1R)-1-(N-((1R)-1-benzyl-2-((methylsulfonyl)amino)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-5-methyl-N-methylhex-2-enamide;

3-(1-Aminoethyl)benzoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2R)-2-hydroxypropylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

(4-(1-Aminocyclobutyl)but-2-enoic acid ((1R)-1-(((1R)-1-(1-methylcarbamoyl)-2-phenylethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-(2-thienyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

(2R)-2-(N-[(2R)-2-(N-[(2-Aminobutoxy)acetyl]-N-methylamino)-3-(2-naphthyl)propionyl]-N-methylamino)-N-methyl-3-phenylpropionamide,

(2R)-N-Methyl-2-(N-methyl-N-((2R)-2-(N-methyl-N-(((2S)-pyrrolidin-2-yl)methoxy)acetyl)amino)-3-(2-naphthyl)propionyl)amino)-3-phenylpropionamide,

3-((2R)-2-(N-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-3-phenylpropionylamino)propyl acetate,

30

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(N-((1R)-1-(dimethylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-

2-(2-naphthyl)ethyl)-N-methylamide,

(2R)-N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-
[piperidin-4-yloxy]acetyl)amino)-3-(2-naphthyl) propionamide,

5

N-Methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-2-(N-methyl-N-[(2-
piperidinyl)methoxy]acetyl)amino)-3-(2-naphthyl)propinamide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-
10 naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2-
naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-
naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-
15 methoxyphenyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(1-
naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-
phenylethyl)amide,

20

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-
naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-
naphthyl)ethyl)amide,

25 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2-
naphthyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-
phenylethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-
30 methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-
naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide,

5

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide,

10 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(4-methoxyphenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-
15 (2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(1-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-
(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-
20 methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide,

25

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-(2,3,4,5,6-pentafluorophenyl)-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(4-methoxyphenyl)ethyl)amide,

30 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-(2,3,4,5,6-pentafluorophenyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-{N-[(1R)-2-phenyl-1-(methylcarbamoyl)ethyl]-N-methylcarbamoyl}-2-phenylethyl)amide,

5 1-((2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methyl amino)-3-(2-naphthyl)propionyl-2-benzyl-4-ethylsemi-carbazide,

1-((2S)-2-(N-(2-(((2R)-pyrrolidin-2-yl)methoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl-2-benzyl-4-ethyl semicarbazide,

10

1-((2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-3-(2-naphthyl)propionyl)-2-benzyl-4-ethylsemicarbazide,

15 (2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl) ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Methyl-5-methylaminohex-2-enoic acid

20 N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenyl ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thiophen-2-yl)ethyl
25)carbamoyl)-2-(2-naphthyl)ethyl) amide,

(2E)-5-Amino-5-methylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-(2-phenyl-1-(((tetrahydrofuran-2-yl)methyl)carbamoyl)ethyl)carbamoyl)-2-(1-naphthyl)ethyl)amide,

30

5-Amino-3,5-dimethylhex-2-enoic acid

N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide,

(2E)-5-Amino-5-methylhex-2-enoic acid

5 N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E)-5-Methyl-5-methylaminohex-2-enoic acid

N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,

(2E) 5-Methyl-5-amino-5-methylhex-2-enoic

acid-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(thien-2-yl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

15

5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-2-(3,4-difluorophenyl)-1-methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

20 5-methylamino-hex-2-enoic acid ((1R)-1-(((1R)-2-phenyl-1-ethylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

5-Amino-5-methyl-hex-2-enoic acid ((1R)-1-(((1R)-1-((2S)-

25 2-hydroxypropylcarbamoyl)-2-(3,4-difluorophenyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide,

5-Amino-5-methyl-hex-2-enoic acid

(1-[[2-(2-fluorophenyl)-1-methylcarbamoyl]ethyl)methylcarbamoyl]-2-(2-naphthyl)ethyl)methylamide,

30

(2Z)-5-Amino-3,5-dimethylhex-2-enoic acid

N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-methylcarbamoyl-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide,

- 5 (2R)-2-(N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino)-N-((1R)-1-benzyl-2-(3-cyclopropylthioureido)ethyl)-N-methyl-3-(2-naphthyl)propionamide,

- (2R)-2-(N-[[2-Amino-2-methylpropoxy]acetyl]-N-methylamino)-N-((1R)-1-
10 (dimethylcarbamoyl)-2-phenylethyl)-N-methyl-3-(2-naphthyl)propionamide,

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-2-phenyl-1-((2,2,2-trifluoroethyl)carbamoyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide, and its acetate salt;

15

(2E)-5-Amino-5-methylhex-2-enoic acid

N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

- 20 (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-2-(3,4-difluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

- (2E)-4-(1-Aminocyclobutyl)but-2-enoic acid N-((1R)-1-(N-((1R)-1-(cyclopropylcarbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-
25 N-methylamide;

(2E) 4-(1-Aminocyclobutyl)-but-2-enoic acid N-((1R)-2-(biphenyl-4-yl)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)ethyl)-N-methylamide;

30

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(2-

naphthyl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

5

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
10 N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(2-naphthyl)propionamide;

15 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-
yl)ethyl)-benzamide;

3-(1-Aminomethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-
yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-
25 yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-
yl)propionamide;

30

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzo[b]thiophen-3-

yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-
5 (benzo[b]thiophen-3-yl)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-
(benzyloxy)ethyl)benzamide;

10

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-(2-thienyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-(((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
15 (methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

20 (2R)-2-(N-(((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-
1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(benzyloxy)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-
25 (benzyloxy)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(2-thienyl)ethyl)-carbamoyl)-2-(biphenyl-4-
yl)ethyl)benzamide;

30

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

- 5 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

- (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
10 ((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;

- 15 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

- 20 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

- 25 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

- 30 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(2-naphthyl)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-benzamide;

5

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

10 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

15

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

20

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

25

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

30

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

5 (2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(benzyloxy)propionamide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

15 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(2-fluorophenyl)ethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)amide;

30 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-

yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)benzamide;

5

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
10 N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-
yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
(1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzo[b]thiophen-3-
15 yl)propionamide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
(1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzo[b]thiophen-3-
yl)ethyl)amide;

20

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
25 2-phenylethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

30 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(benzyloxy)propionamide;

5 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(biphenyl-4-
yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
10 2-phenylethyl)carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

15 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(biphenyl-4-yl)propionamide;

20

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(2-
naphthyl)ethyl)benzamide;

25 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propionamide;

30

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)-

propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(2-naphthyl)propion-
5 amide;

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(2-
naphthyl)-ethyl)amide;

10

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-
(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-
(benzo[b]thiophen-3-yl)ethyl)-benzamide;

15 3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-
2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(benzo[b]thiophen-3-yl)ethyl)-
benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-
20 (methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-3-
yl)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-
N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-
25 (benzo[b]thiophen-3-yl)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzo[b]thiophen-
3-yl)propionamide;

30

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-
((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-

(benzo[b]thiophen-3-yl)ethyl)amide;

3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-

5 (benzyloxy)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(benzyloxy)ethyl)benzamide;

10 (2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

(2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-

15 (benzyloxy)propionamide;

(2R)-2-(N-((2-Amino-2-methylpropoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(benzyloxy)propionamide;

20

(2E)-5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)carbamoyl)-2-(benzyloxy)ethyl)amide;

25 3-(1-Aminoethyl)-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)-ethyl)carbamoyl)-2-(biphen-4-yl)ethyl)benzamide;

3-Aminomethyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-

30 2-(4-methoxyphenyl)ethyl)-carbamoyl)-2-(biphenyl-4-yl)ethyl)benzamide;

(2R)-2-(N-((2-Aminobutoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

5 (2R)-2-(N-(((2S)-2-Pyrrolidinyl)methoxy)acetyl)-N-methylamino)-N-methyl-N-((1R)-1-(methylcarbamoyl)-2-(4-methoxyphenyl)ethyl)-3-(biphenyl-4-yl)propionamide;

(2E)-5-Amino-5-methyl-N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-((N-methyl-
10 N-(methylsulfonyl)amino)methyl)-2-(2-thienyl)ethyl)carbamoyl)-2-(2-naphthyl)ethyl)hex-2-enamide;

(2E)-5-Amino-5-methylhex-2-enoic acid
N-((1R)-1-(N-((1R)-1-(N-methyl-N-(3-dimethylaminopropyl)carbamoyl)-2-
15 phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

(2E)-5-Amino-5-methylhex-2-enoic acid
N-((1R)-1-(N-((1R)-1-(N-methylcarbamoyl)-2-phenylethyl)-N-ethylcarbamoyl)-2-(2-
naphthyl)ethyl)-N-methylamide;

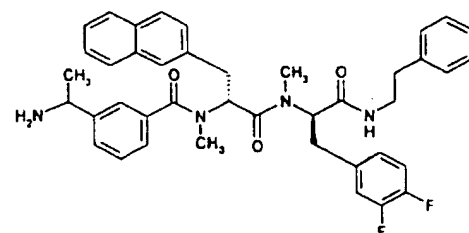
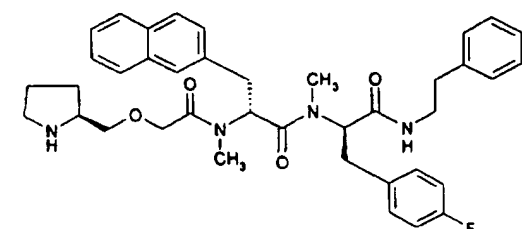
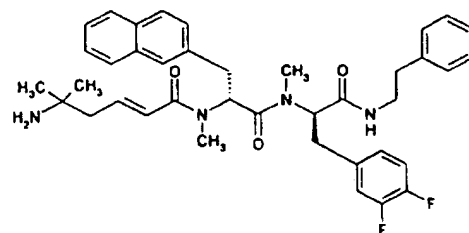
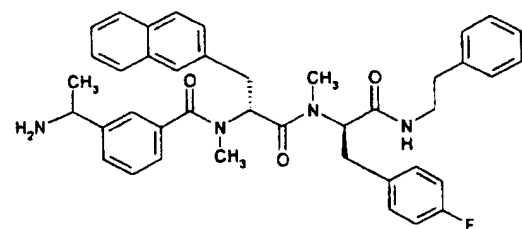
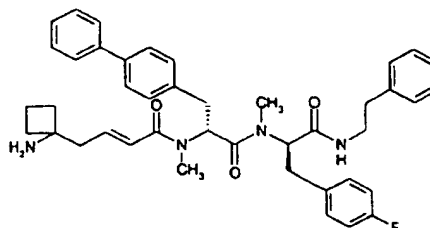
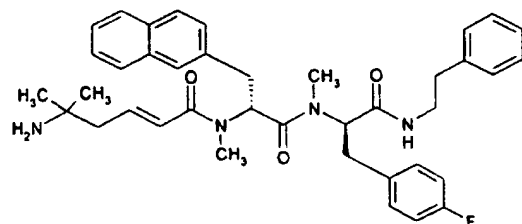
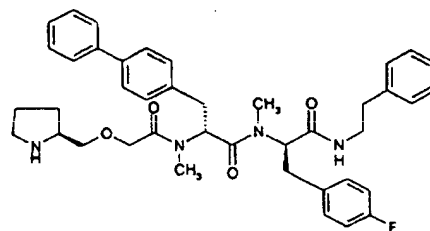
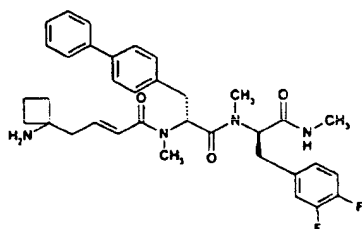
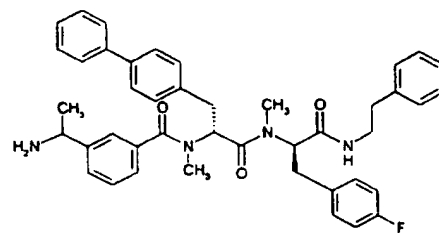
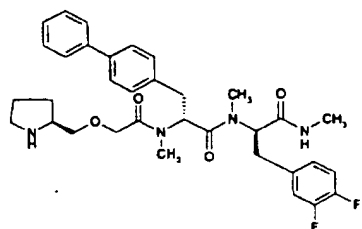
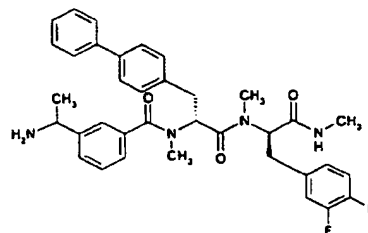
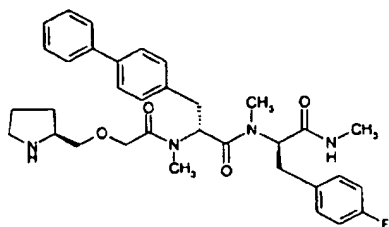
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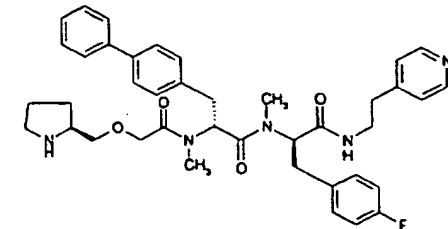
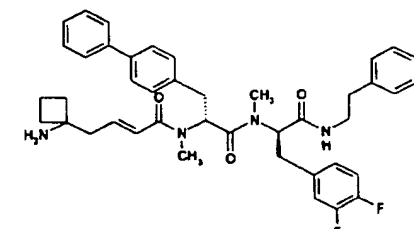
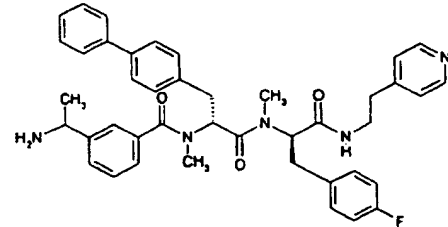
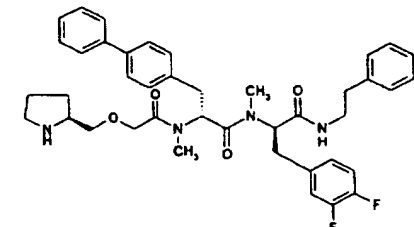
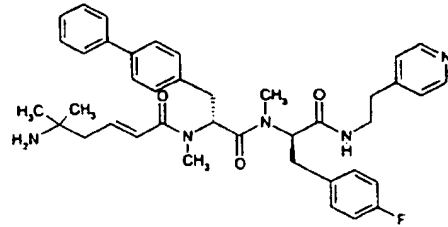
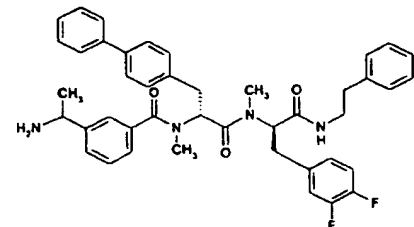
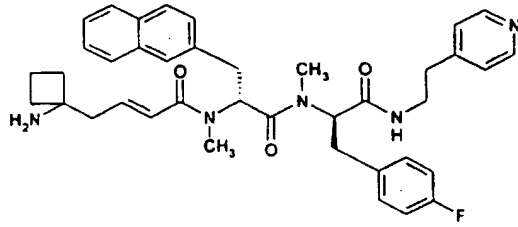
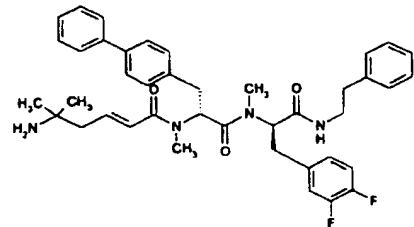
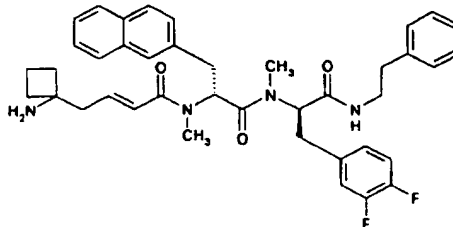
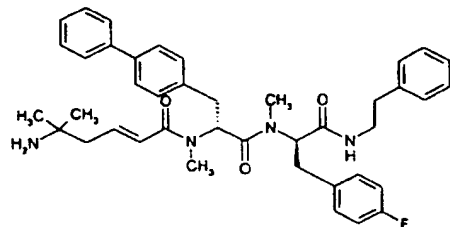
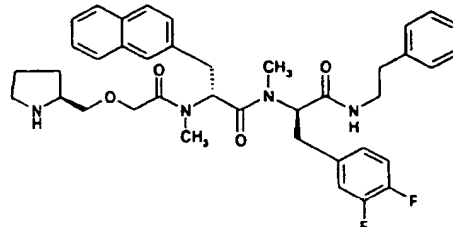
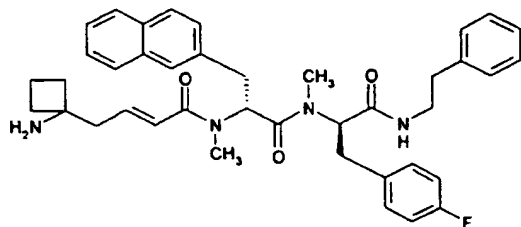
(2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-(N,N-dimethylcarbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide; or

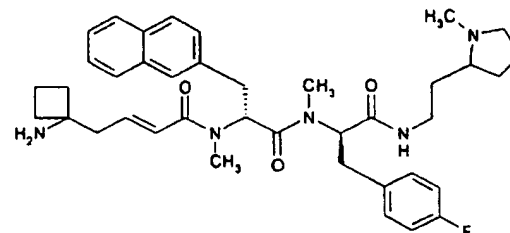
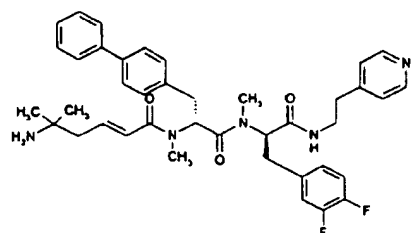
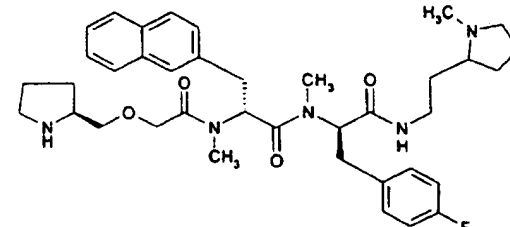
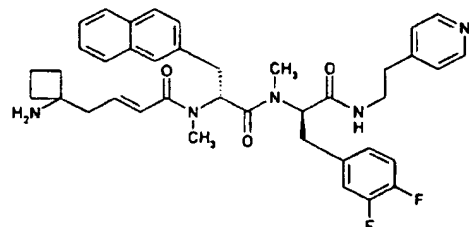
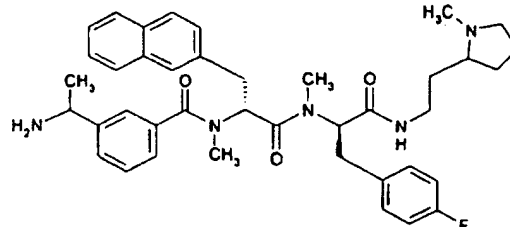
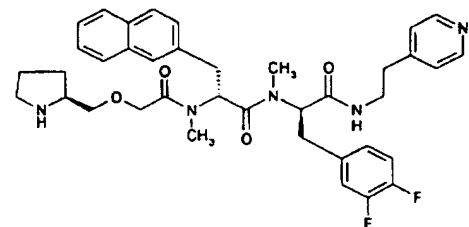
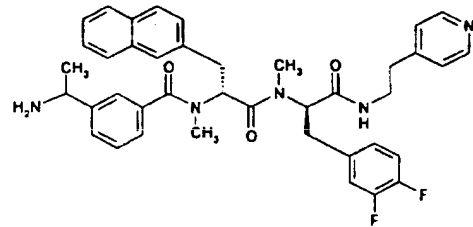
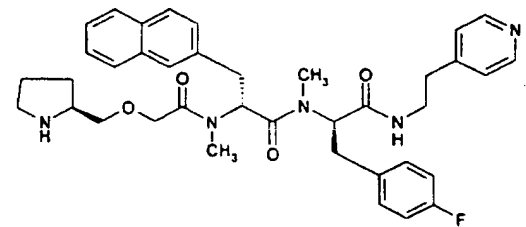
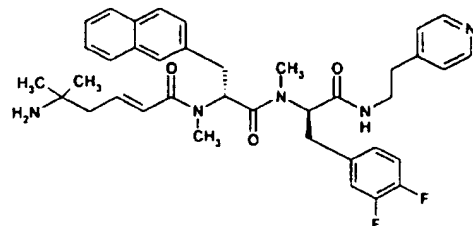
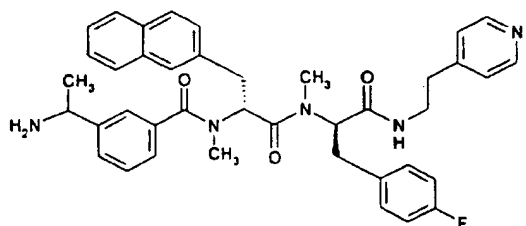
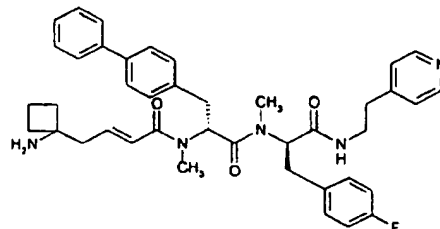
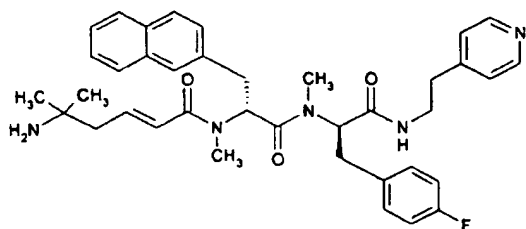
25 (2E)-5-Amino-5-methylhex-2-enoic acid-N-((1R)-1-(N-((1R)-1-(N-(carbamoylmethyl)carbamoyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide;

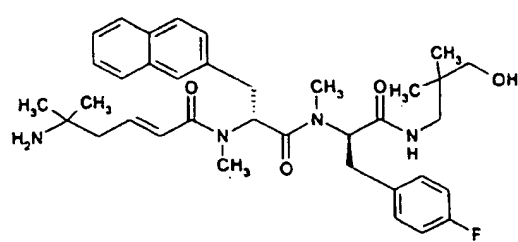
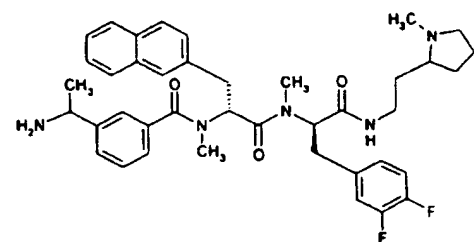
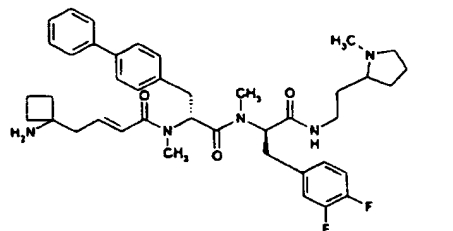
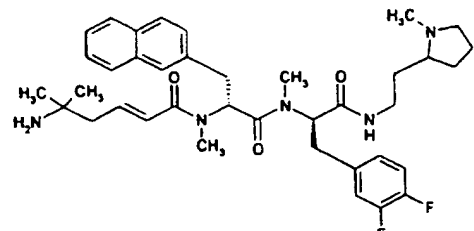
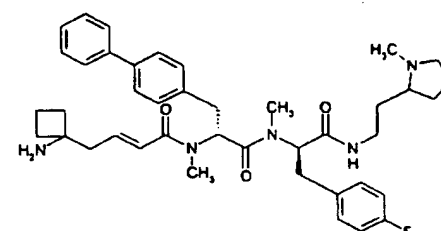
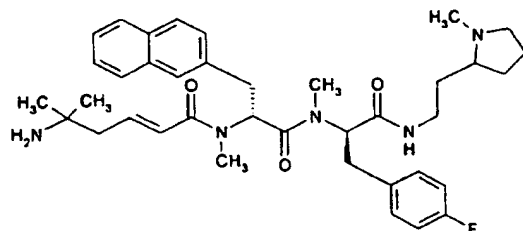
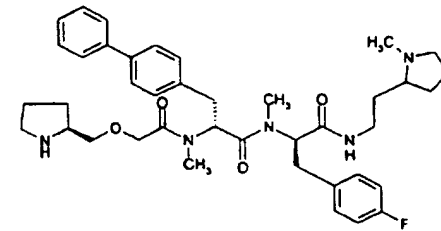
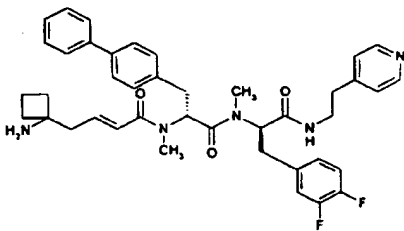
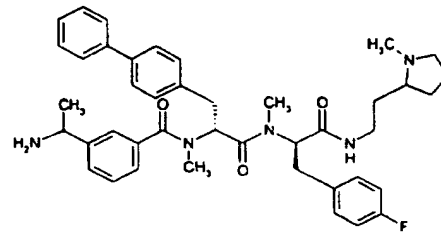
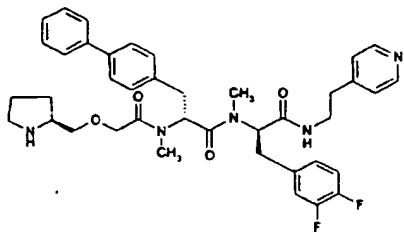
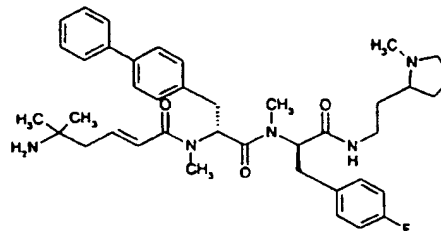
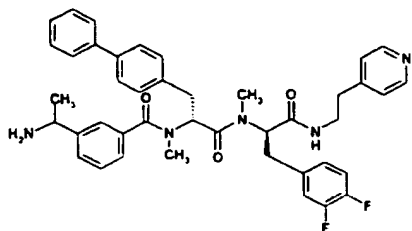
or a pharmaceutically acceptable salt thereof.

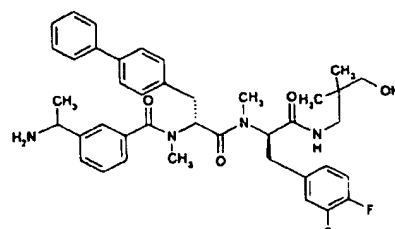
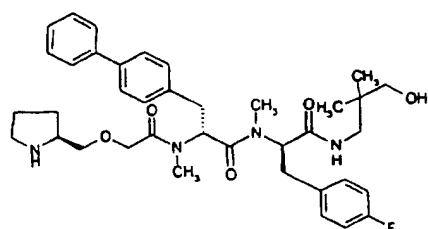
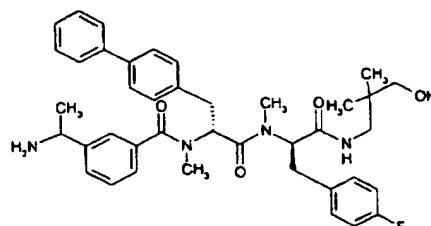
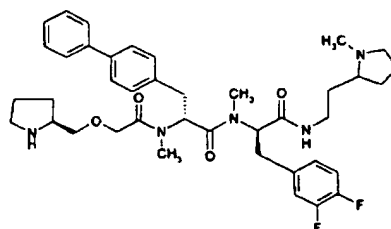
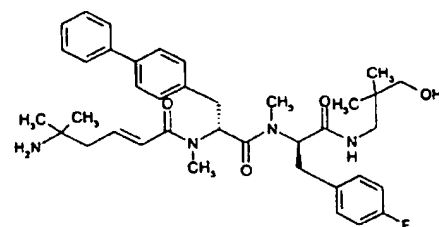
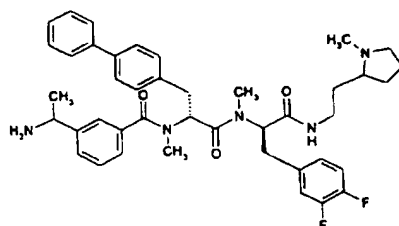
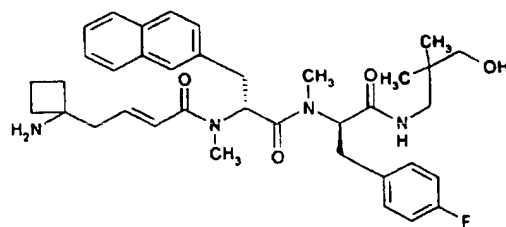
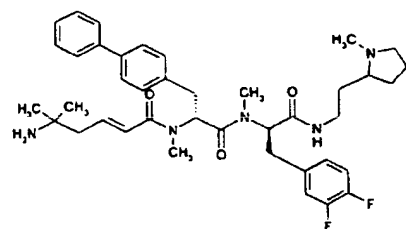
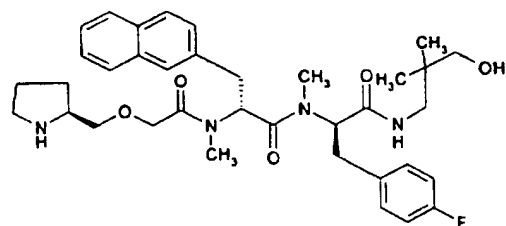
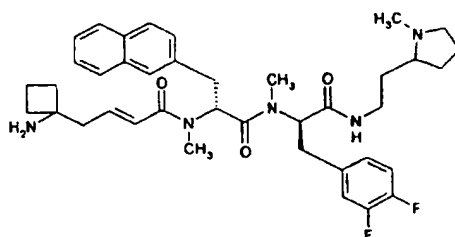
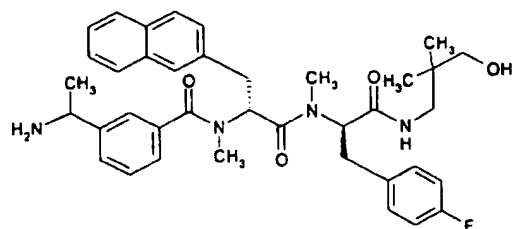
30

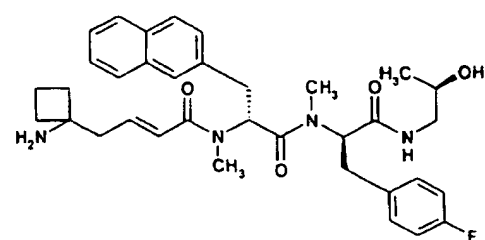
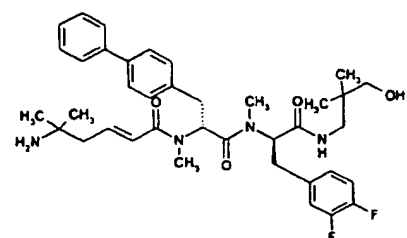
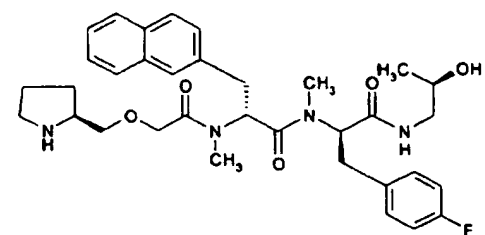
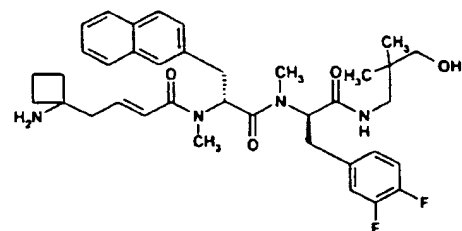
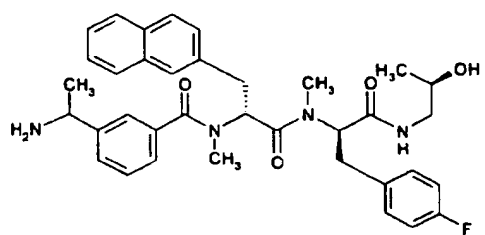
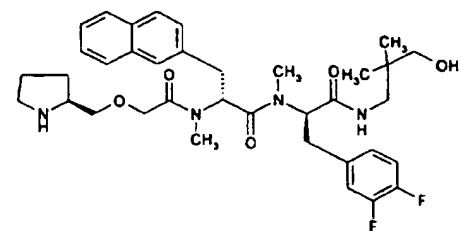
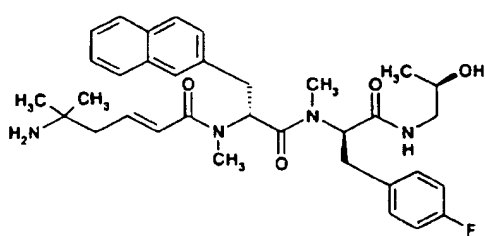
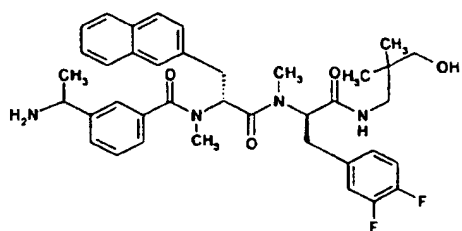
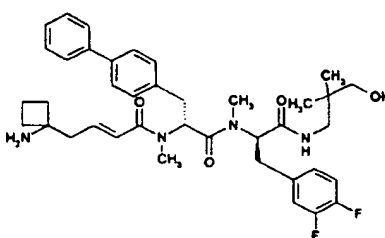
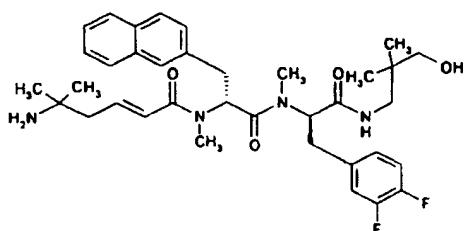
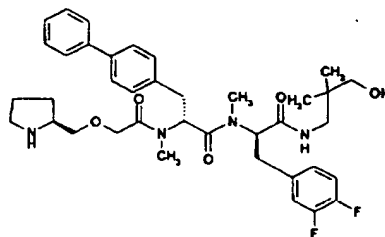
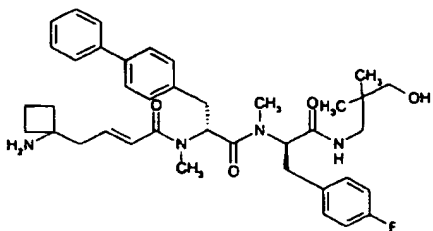


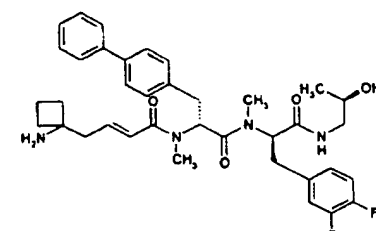
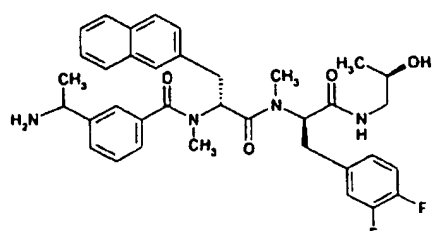
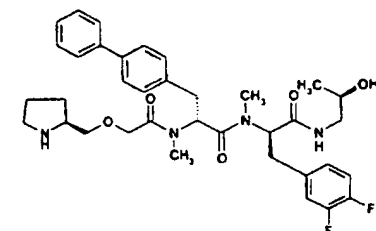
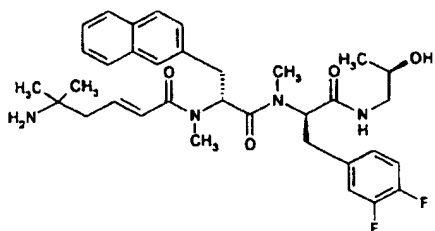
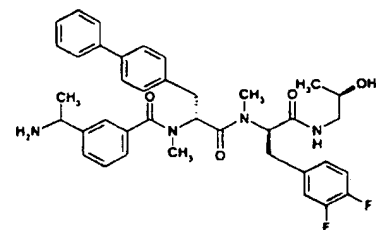
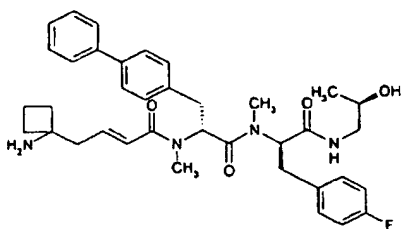
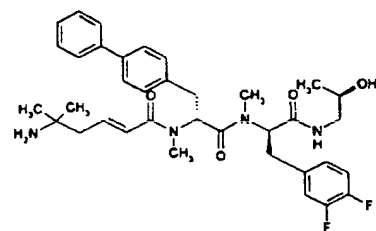
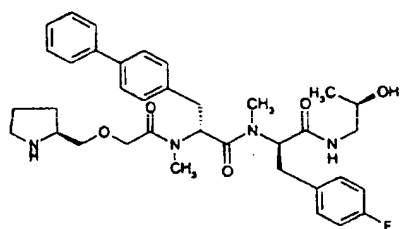
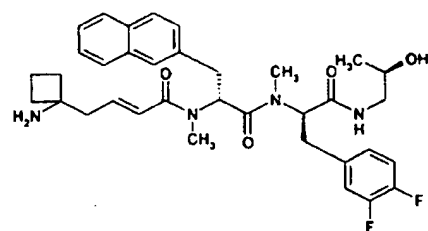
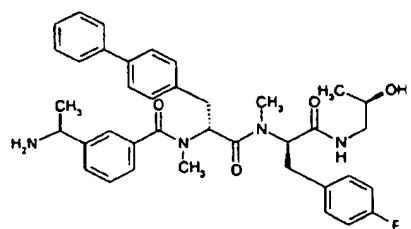
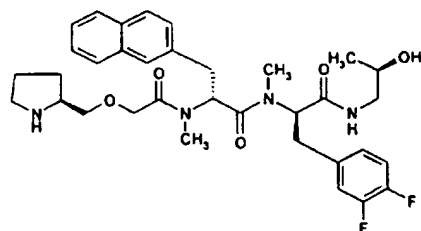
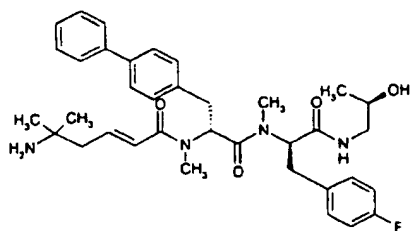


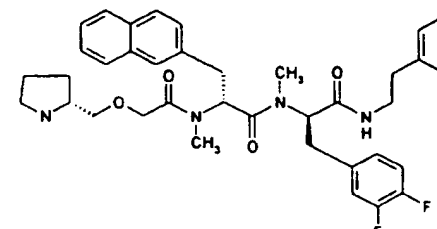
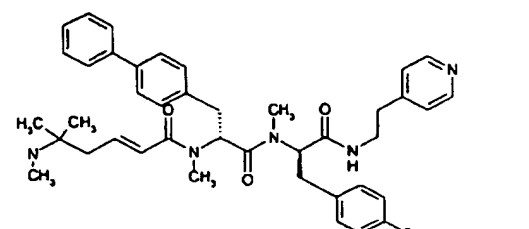
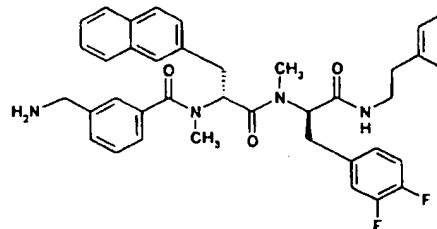
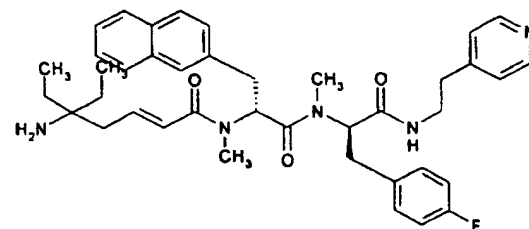
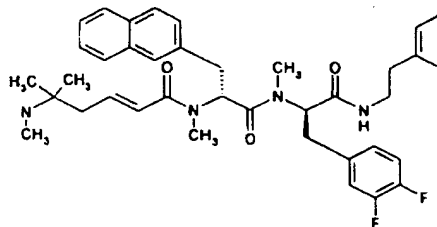
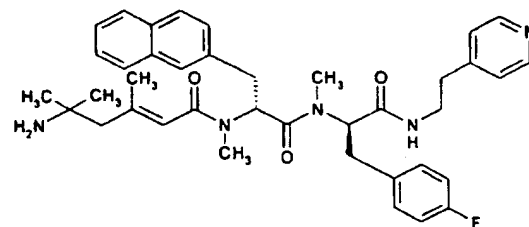
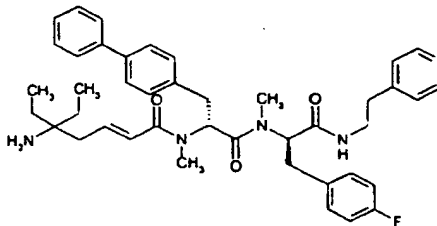
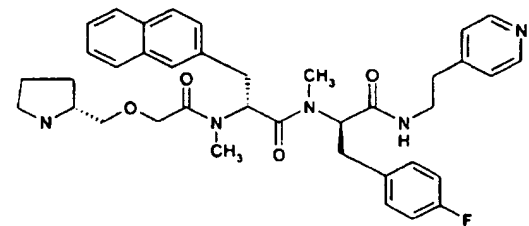
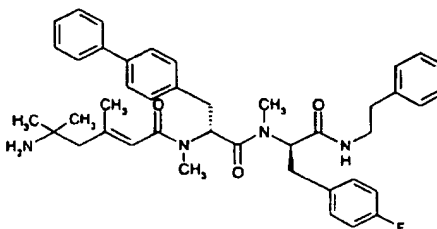
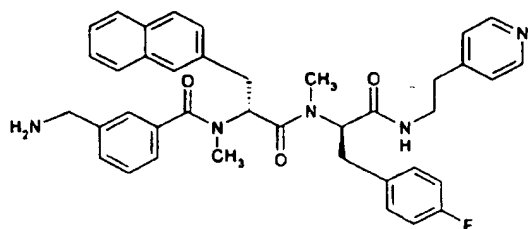
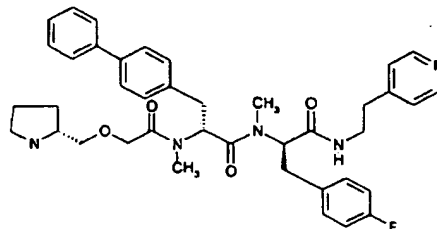
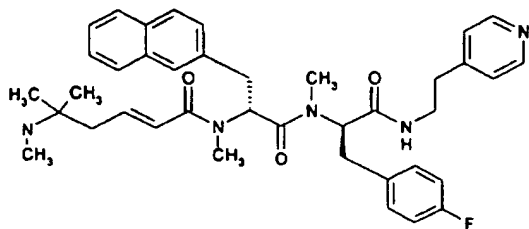


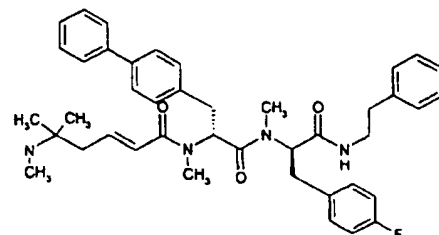
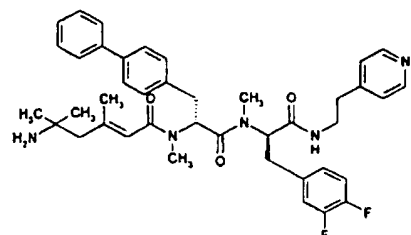
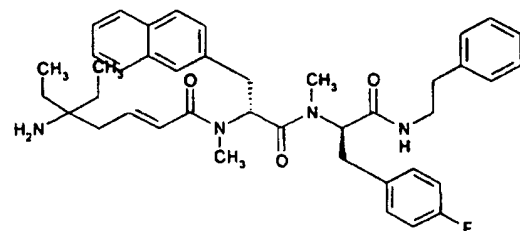
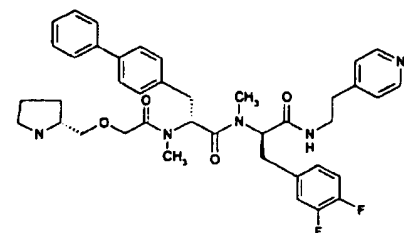
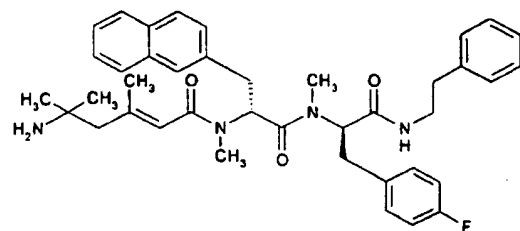
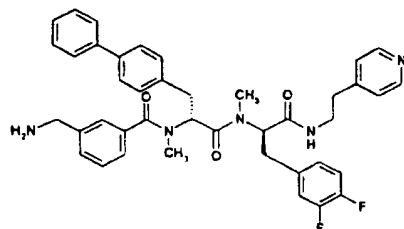
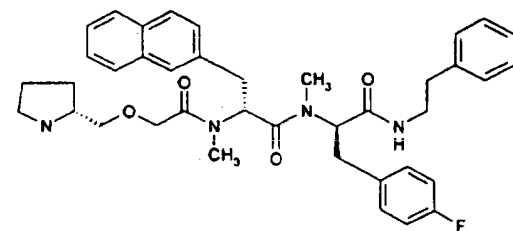
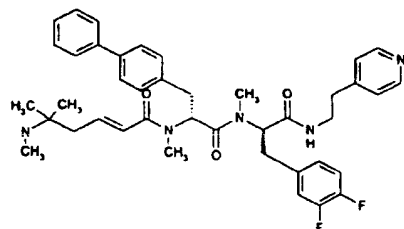
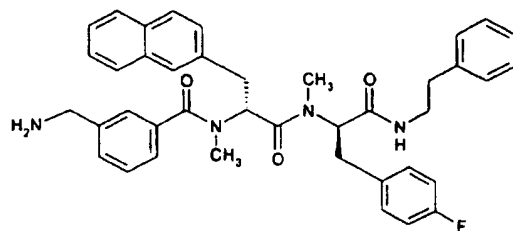
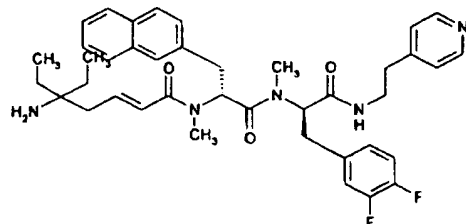
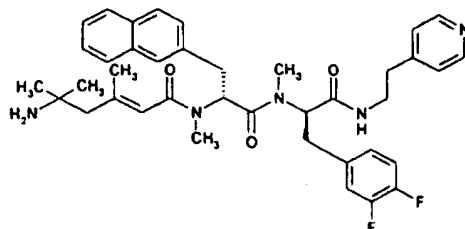
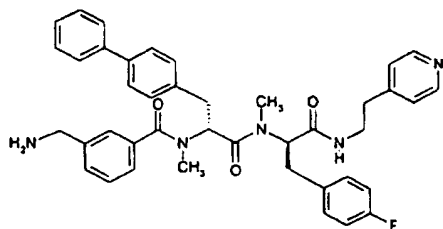


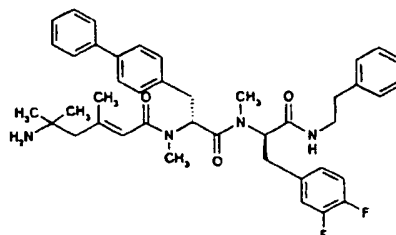
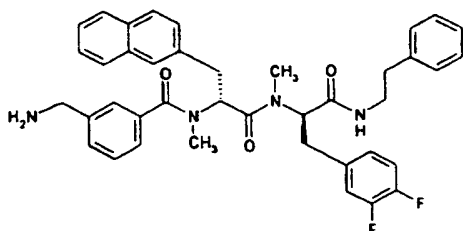
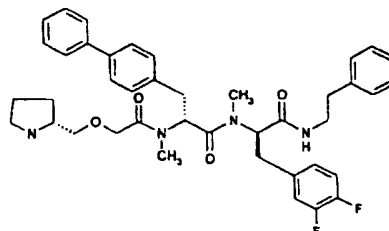
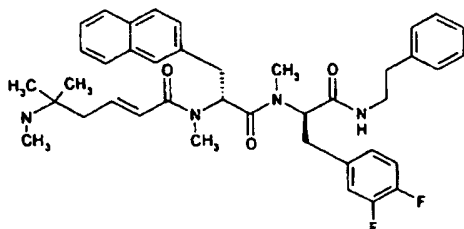
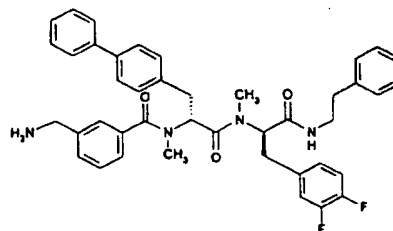
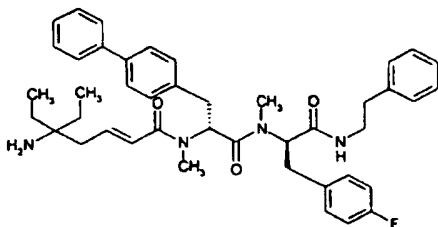
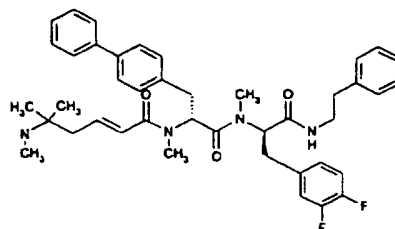
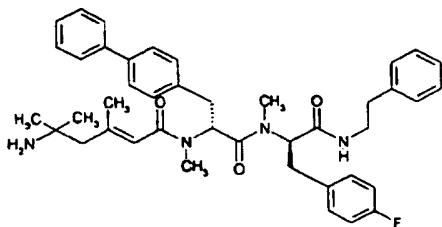
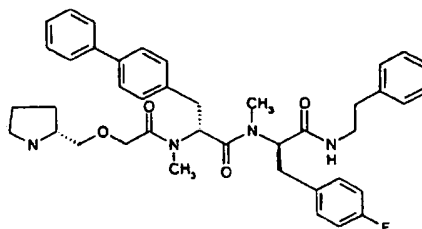
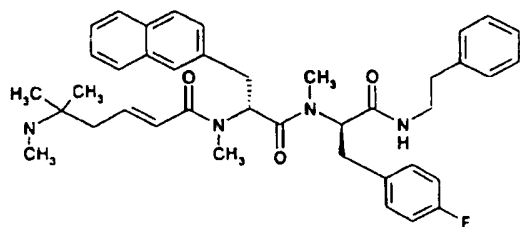
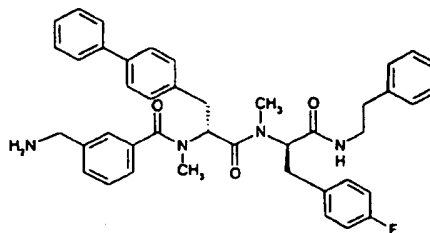
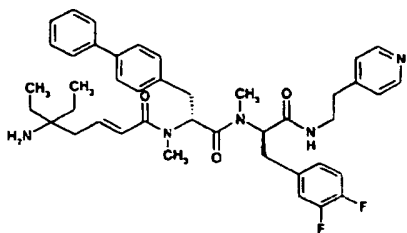


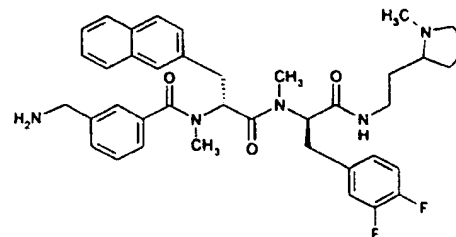
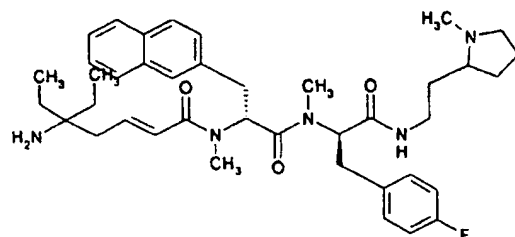
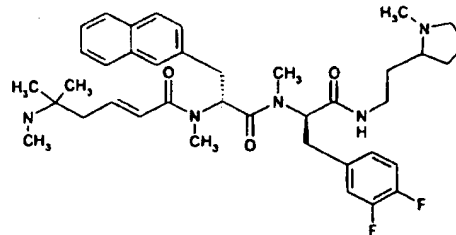
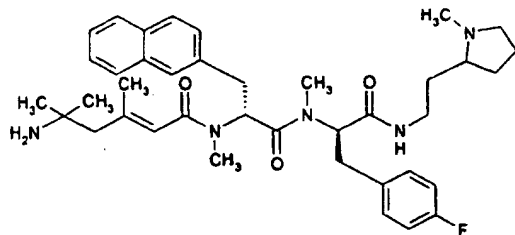
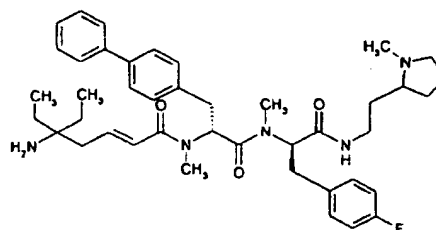
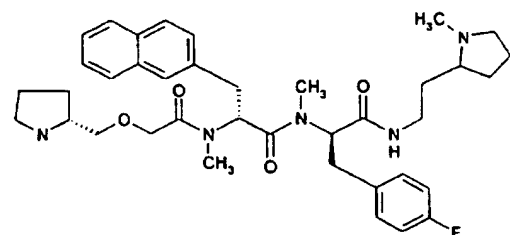
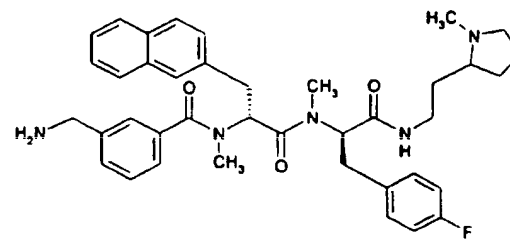
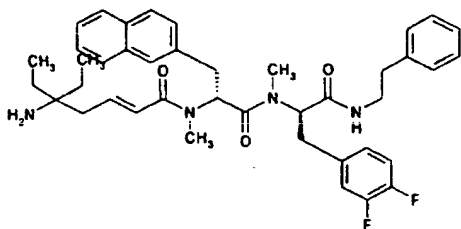
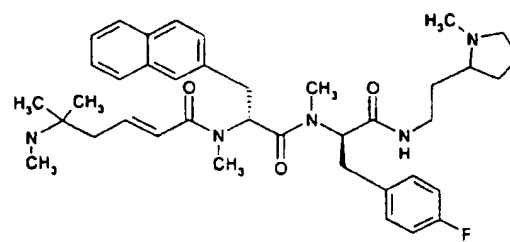
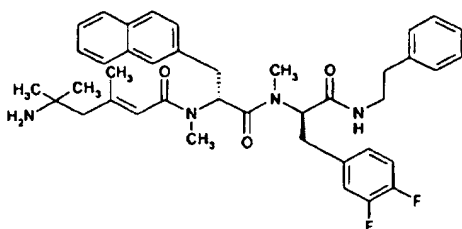
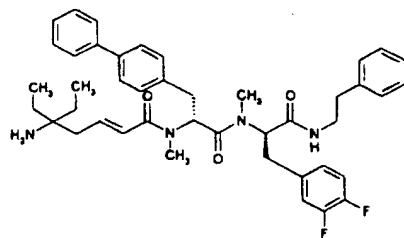
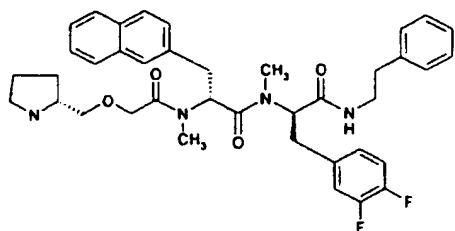


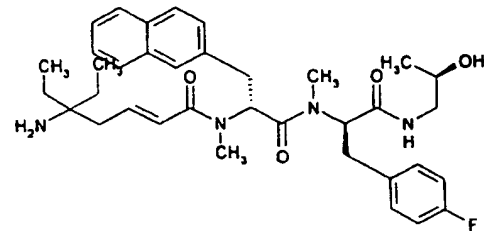
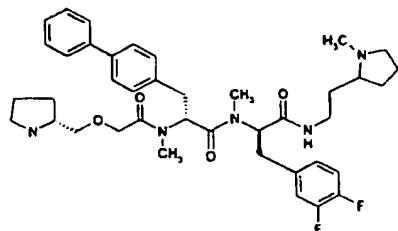
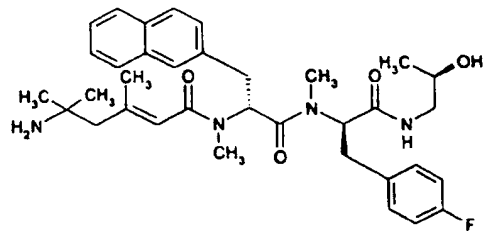
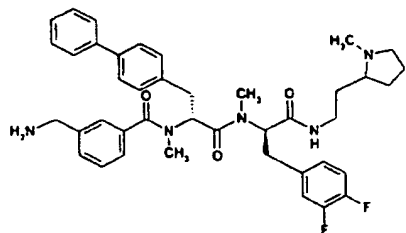
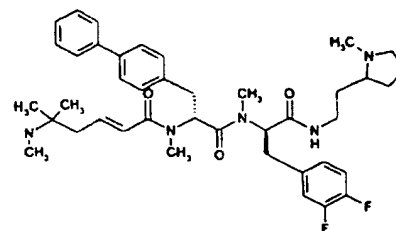
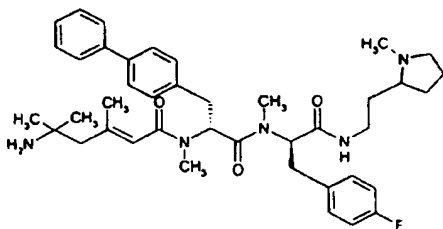
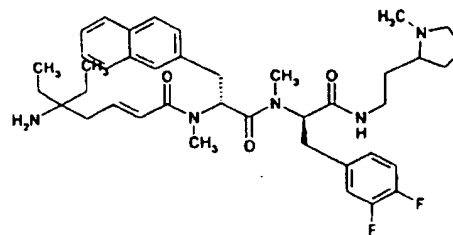
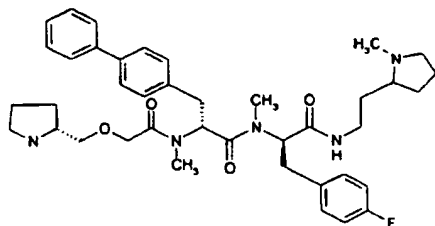
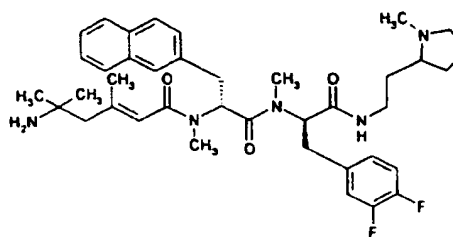
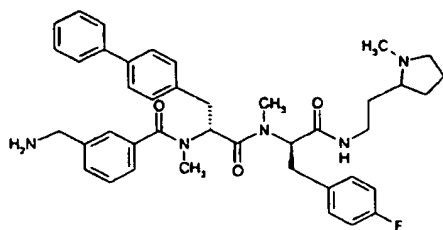
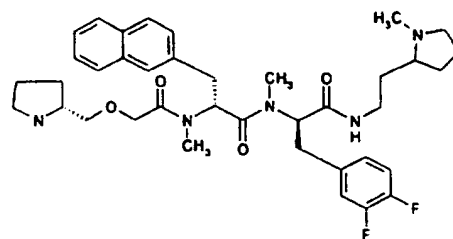
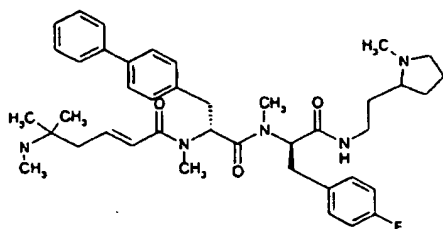


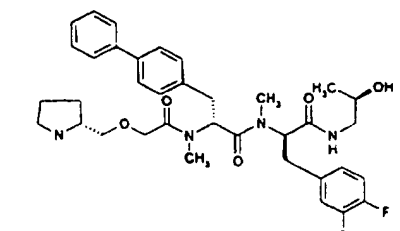
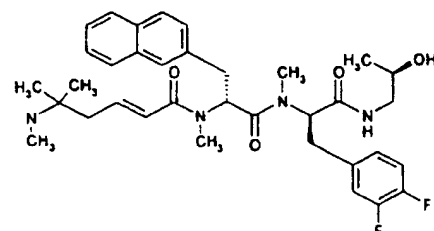
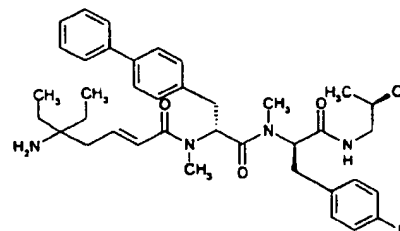
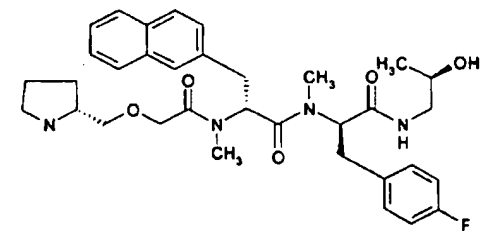
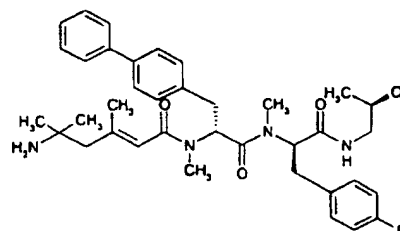
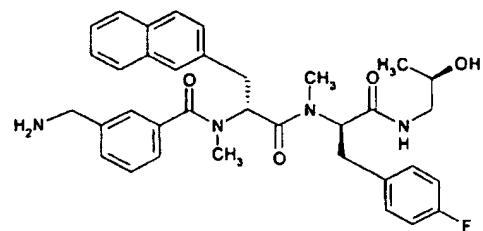
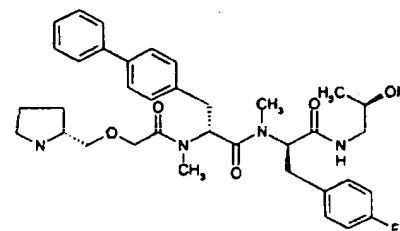
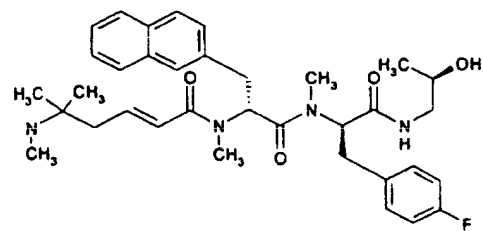
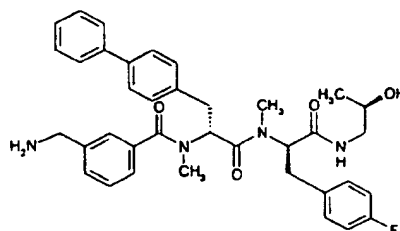
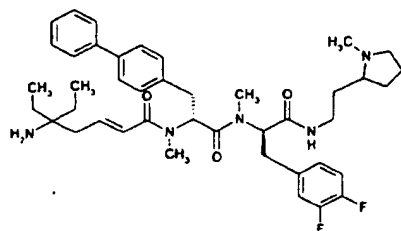
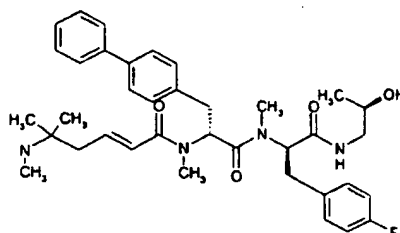
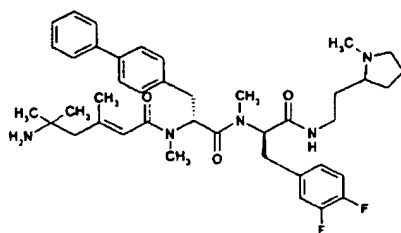


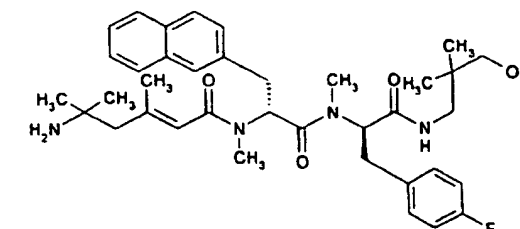
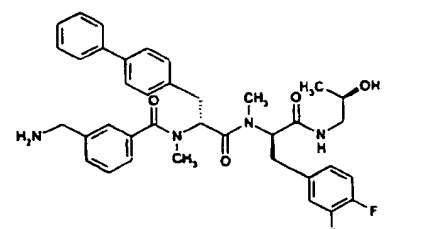
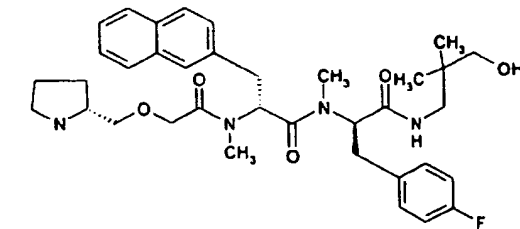
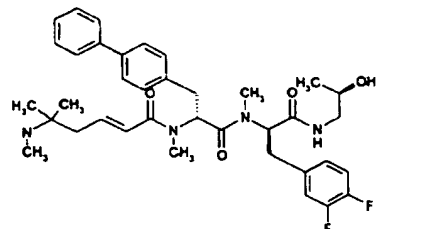
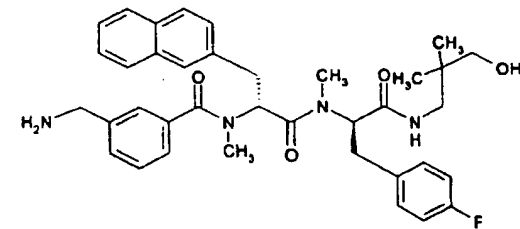
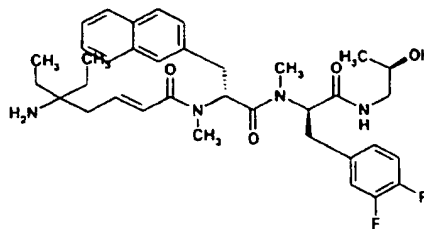
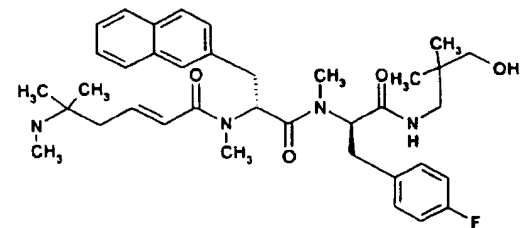
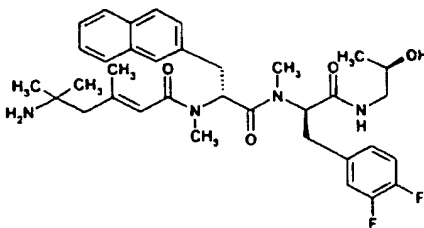
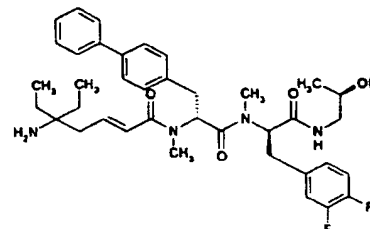
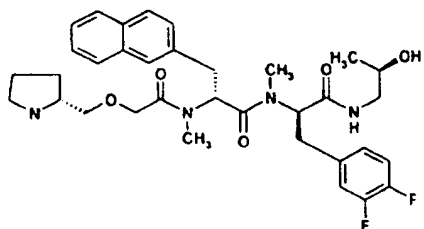
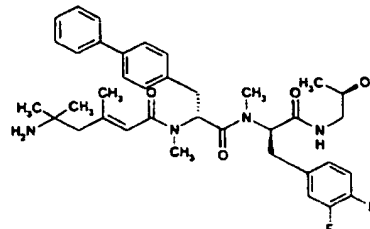
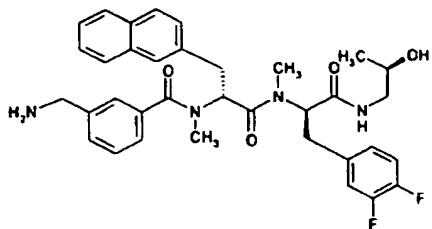


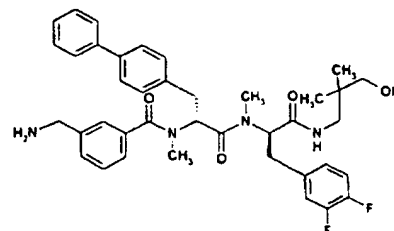
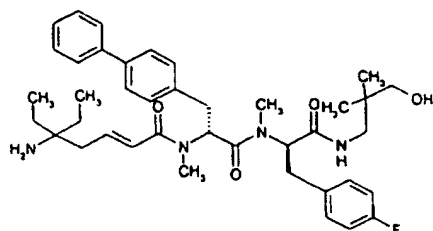
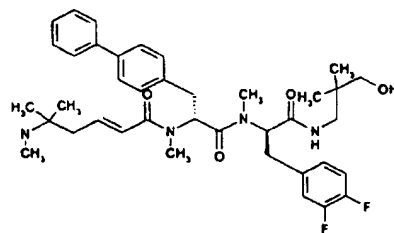
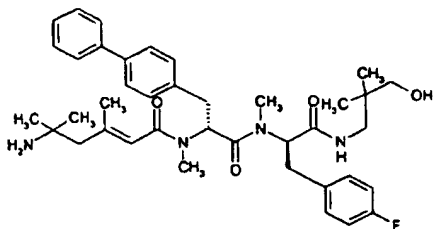
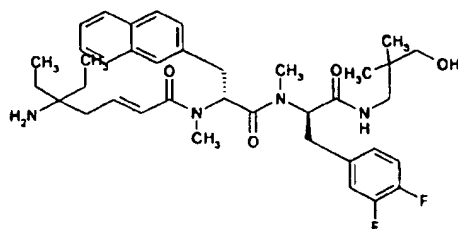
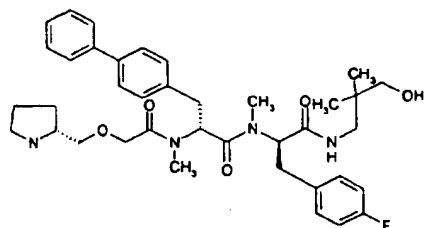
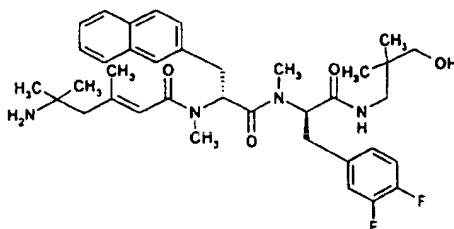
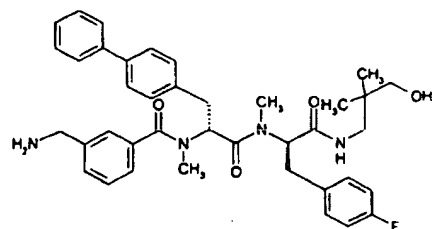
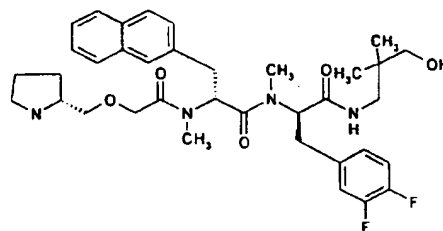
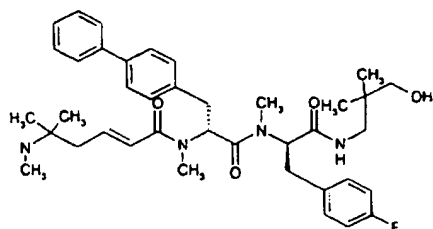
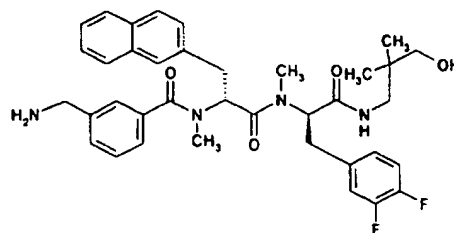
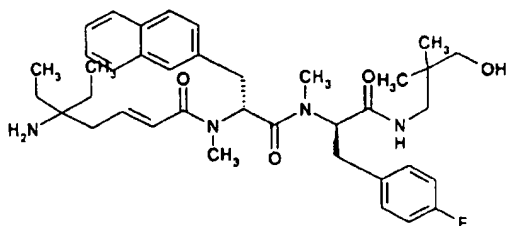


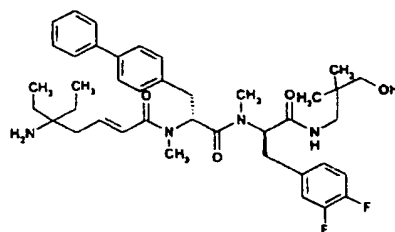
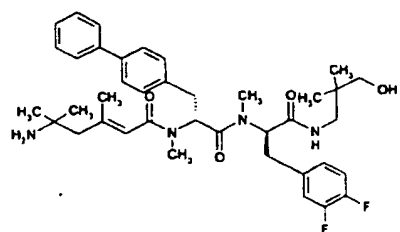
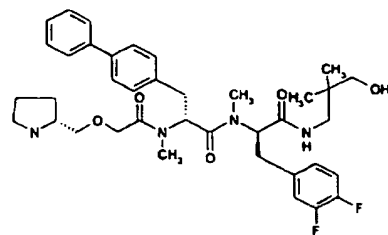
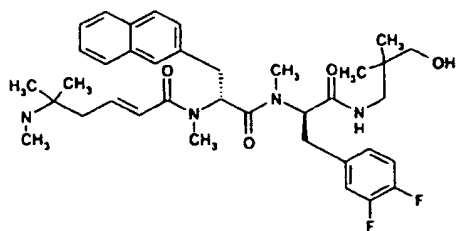


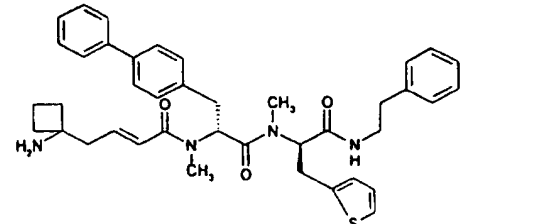
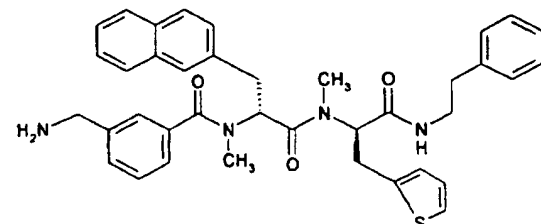
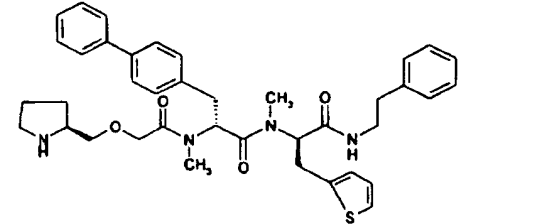
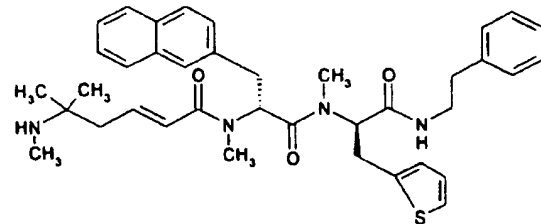
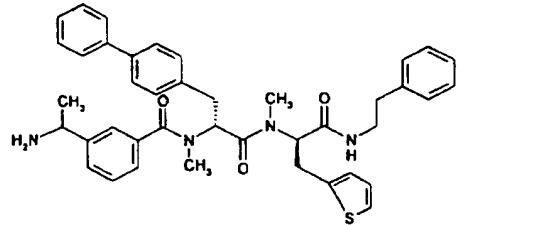
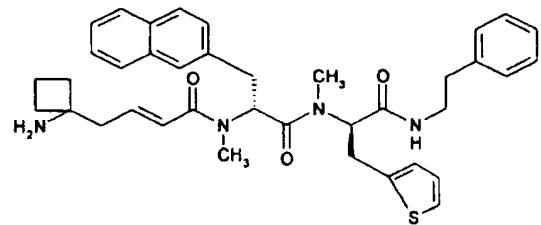
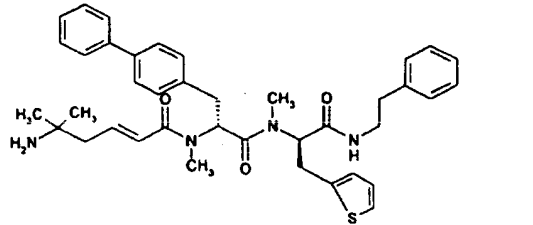
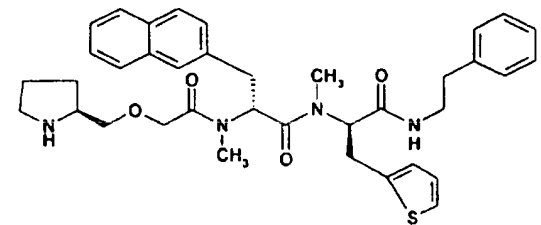
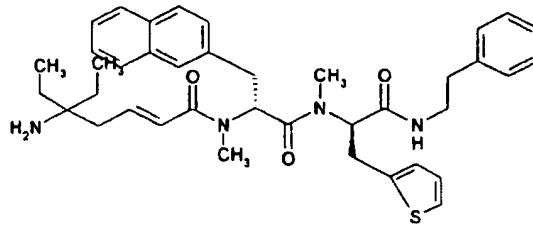
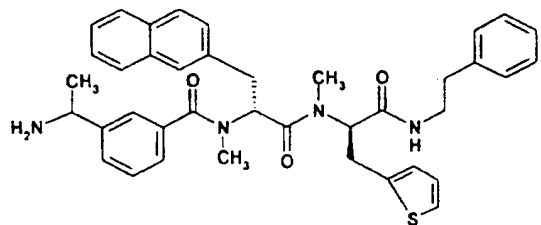
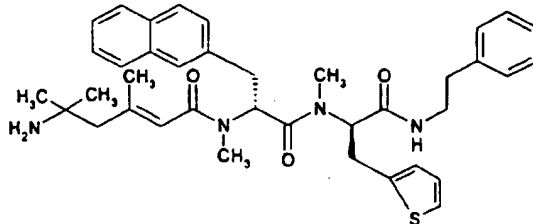
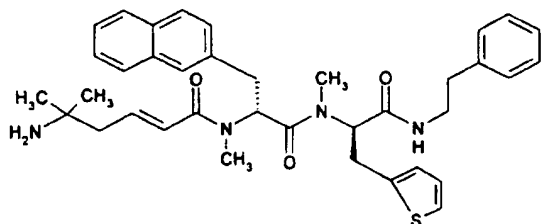


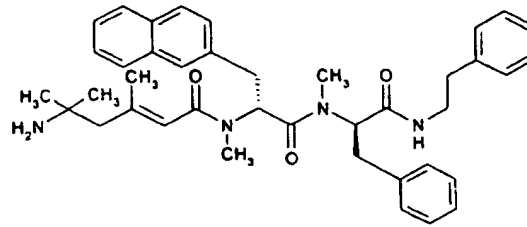
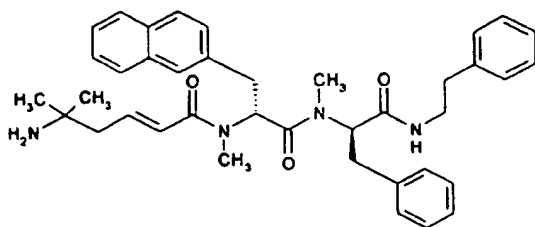
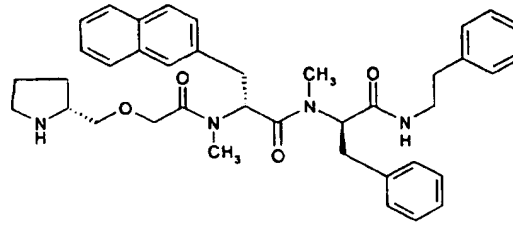
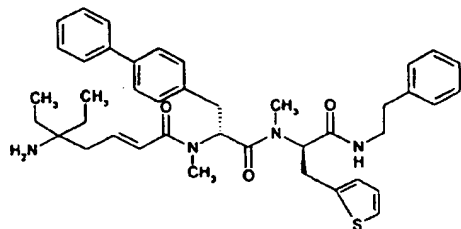
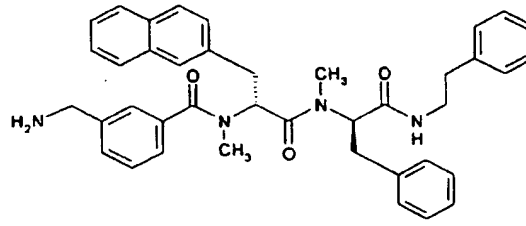
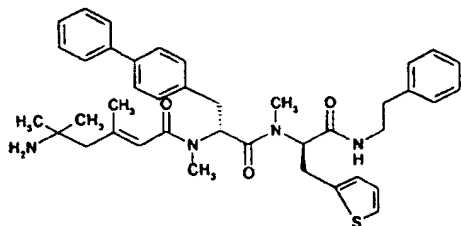
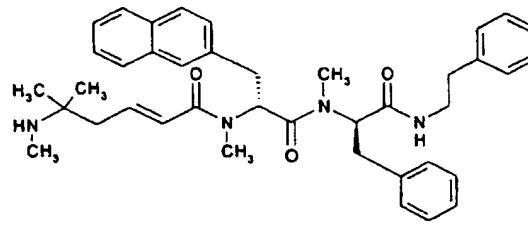
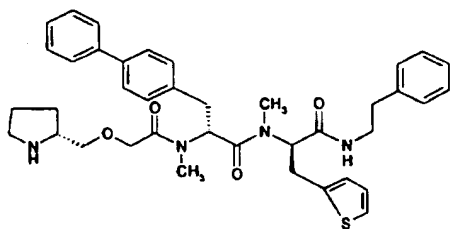
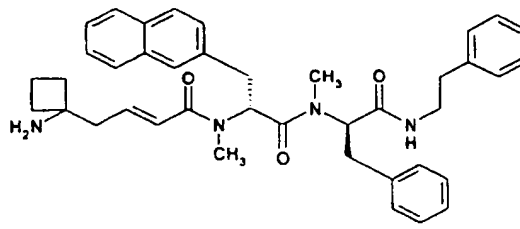
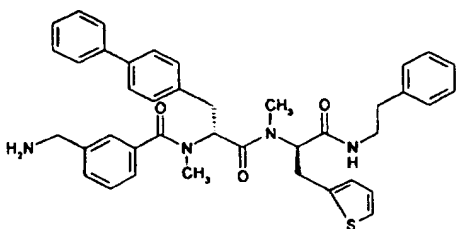
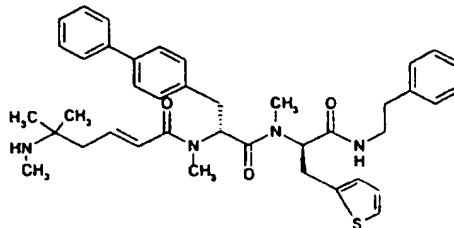


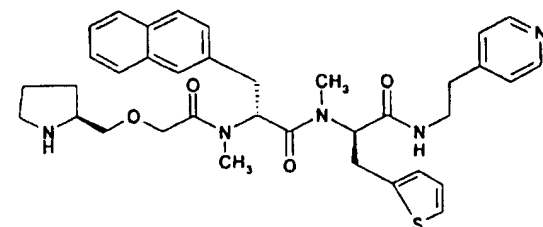
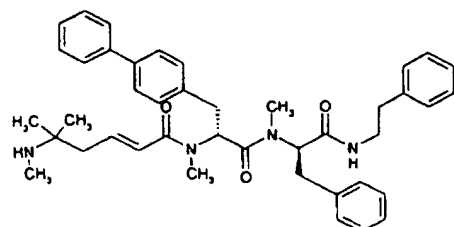
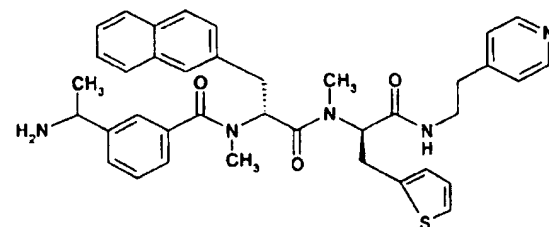
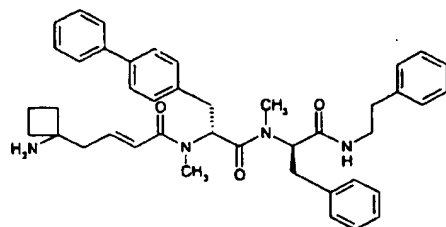
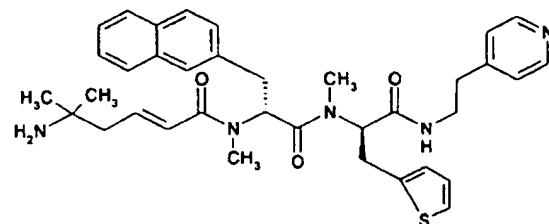
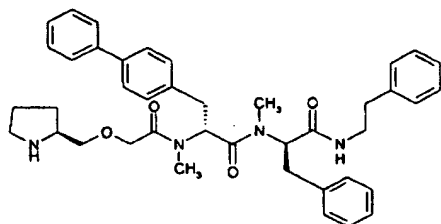
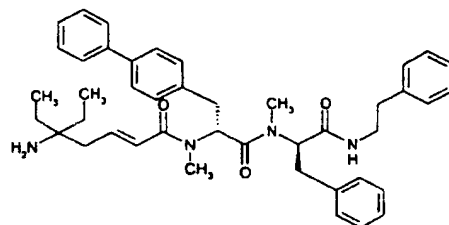
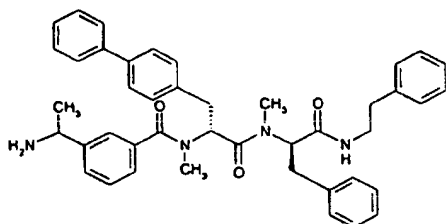
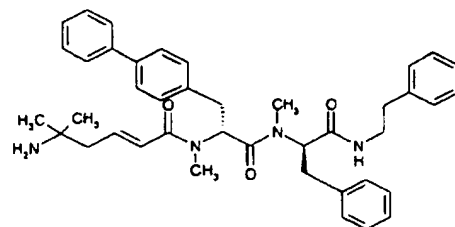
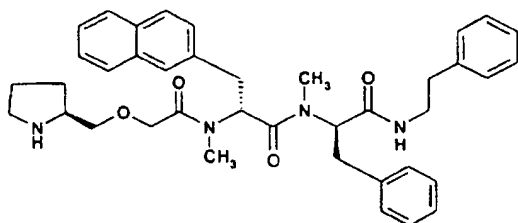
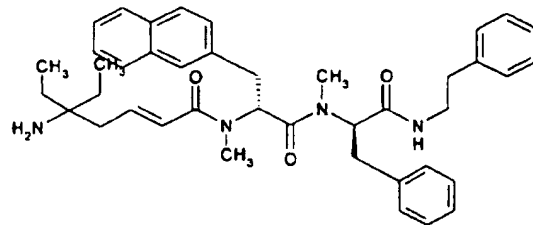
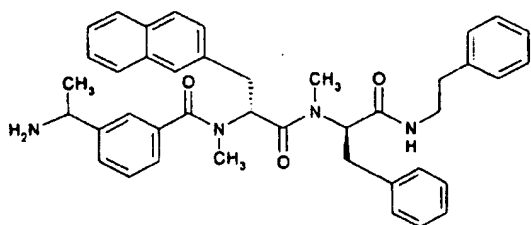


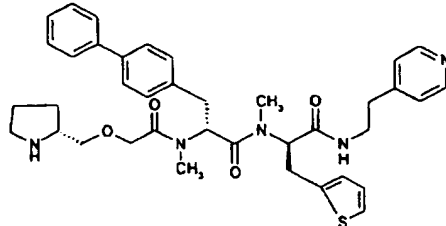
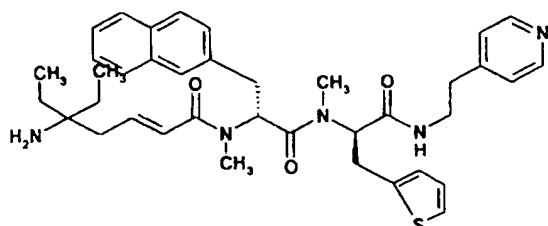
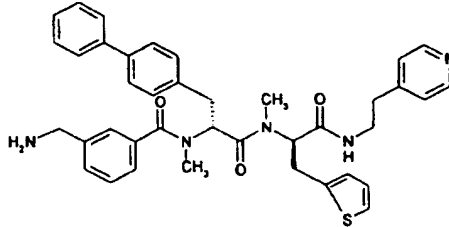
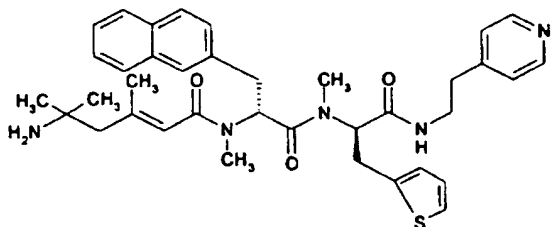
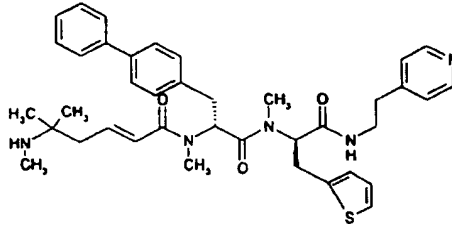
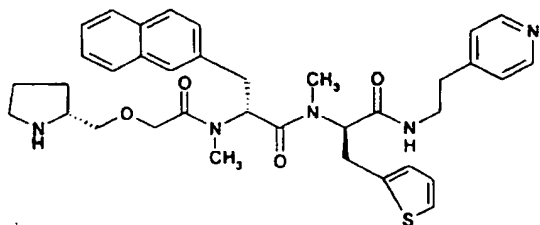
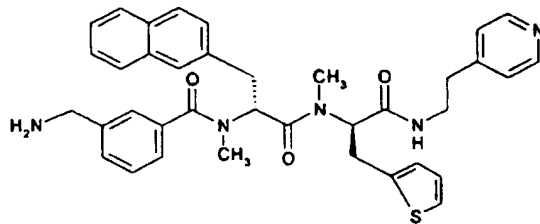
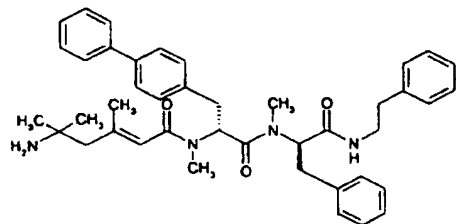
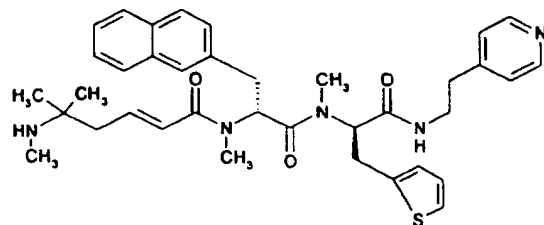
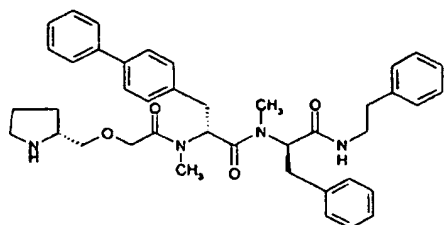
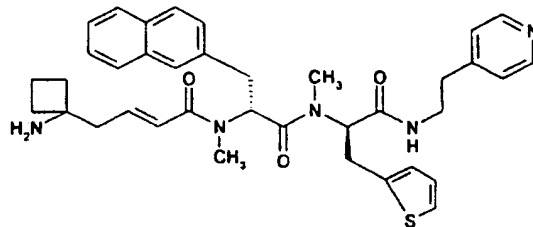
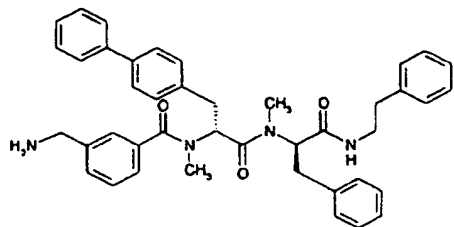


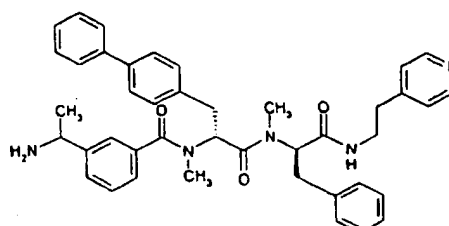
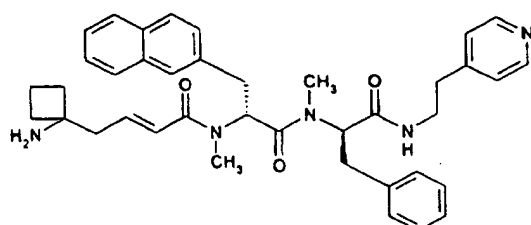
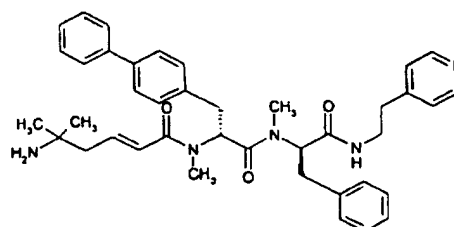
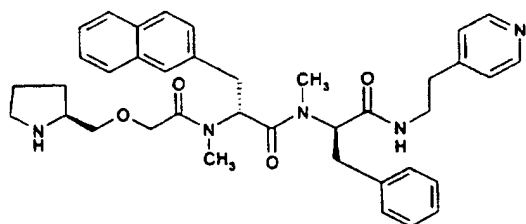
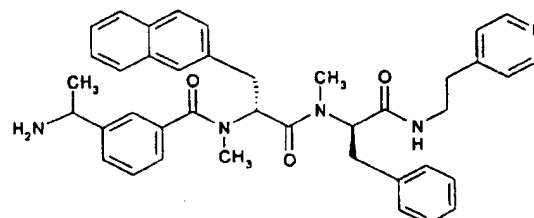
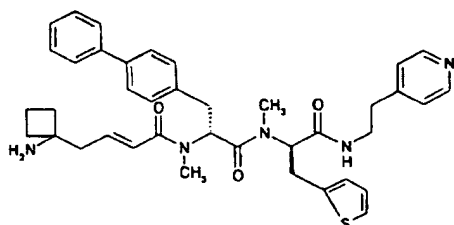
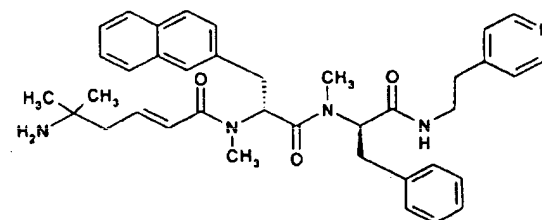
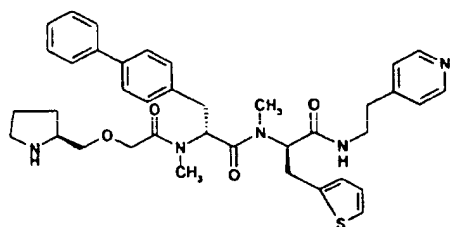
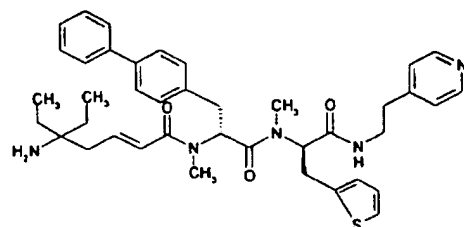
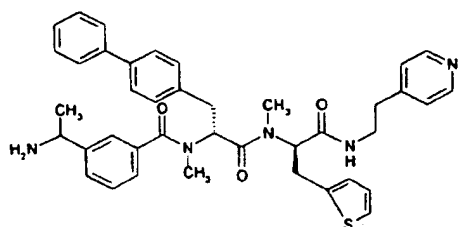
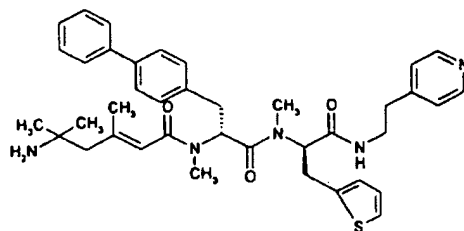
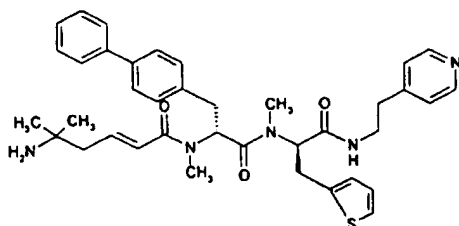


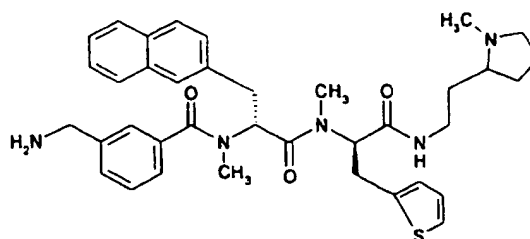
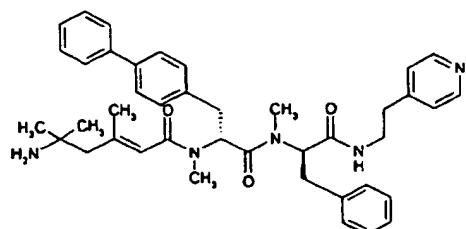
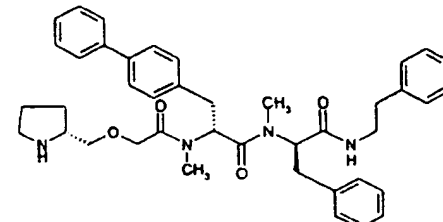
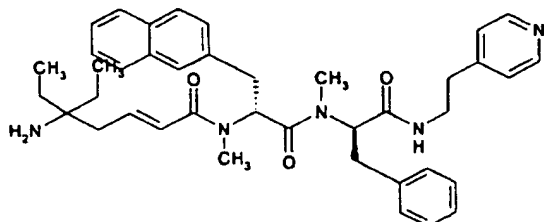
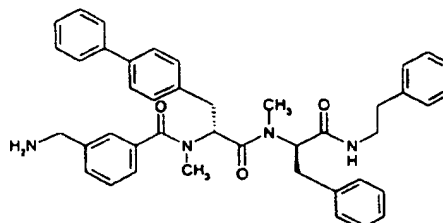
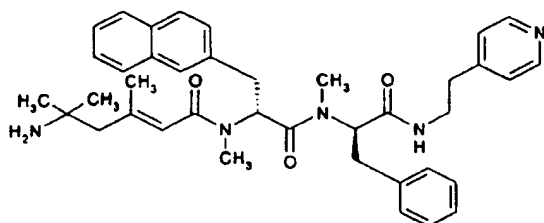
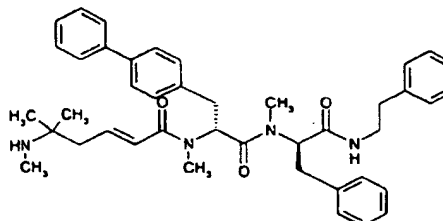
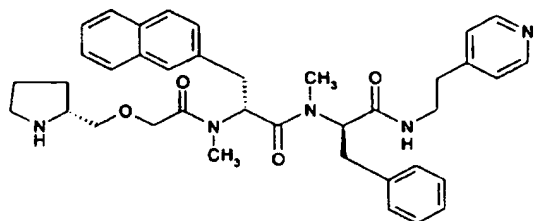
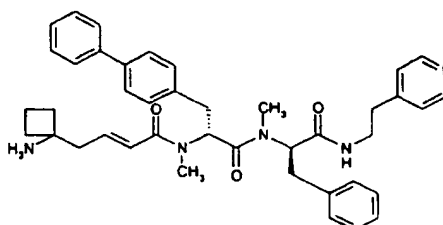
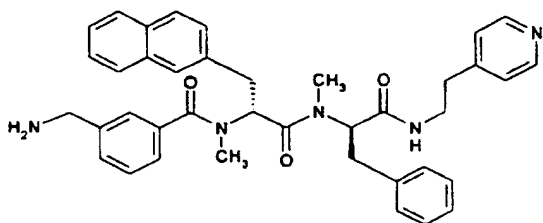
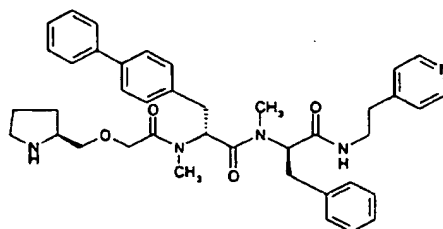
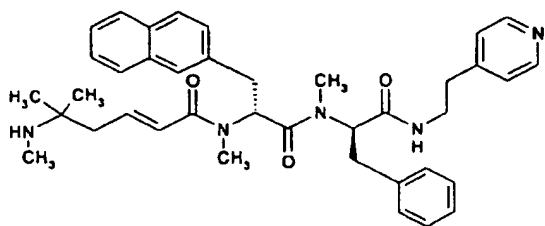


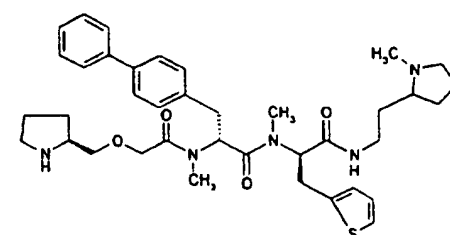
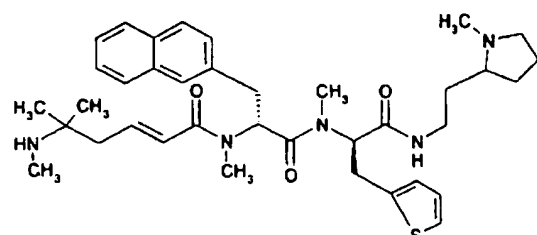
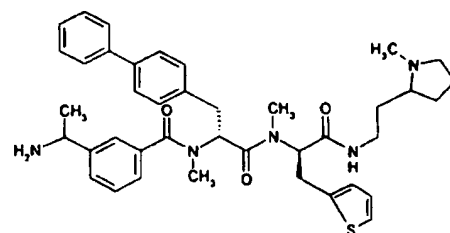
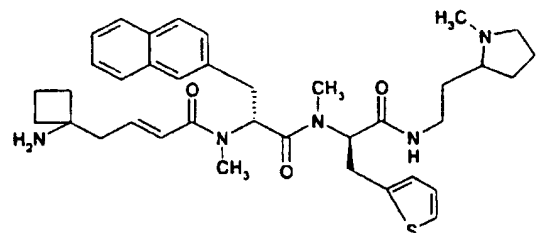
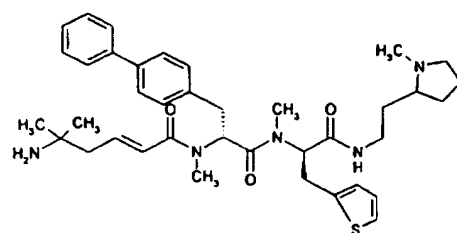
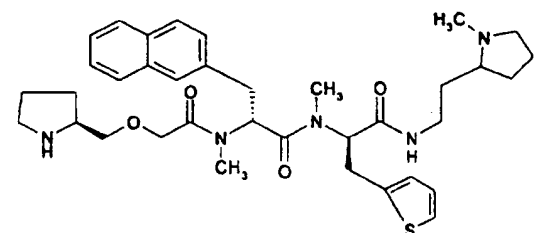
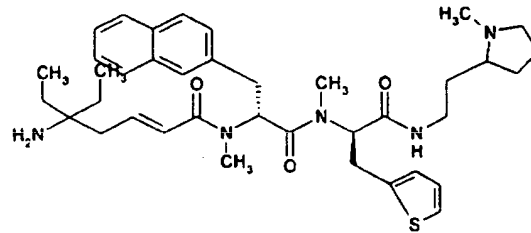
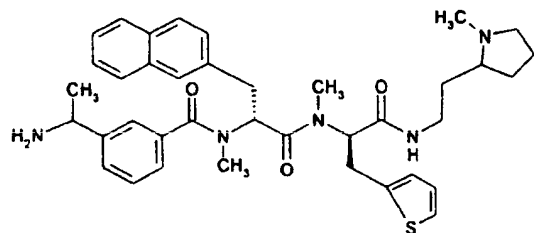
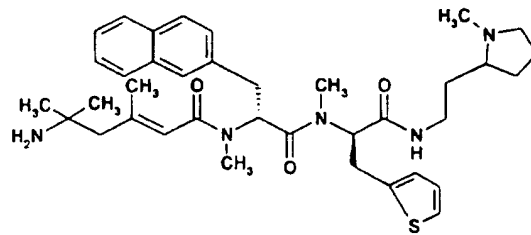
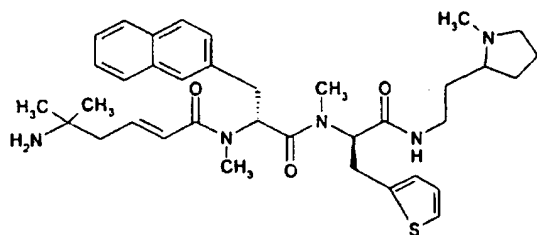
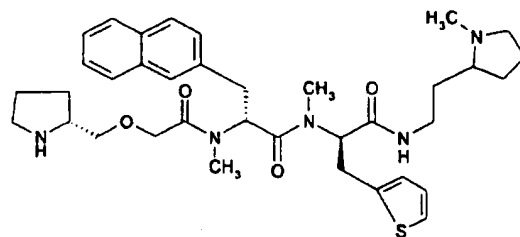
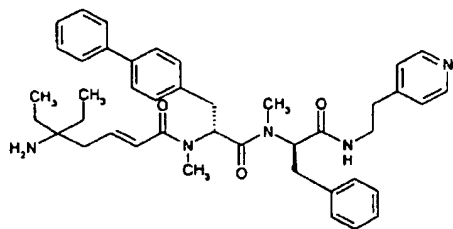


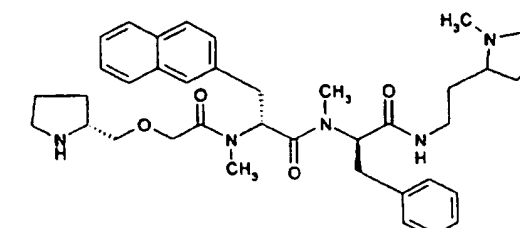
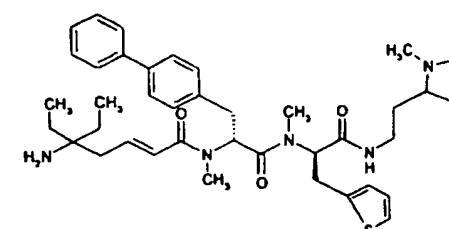
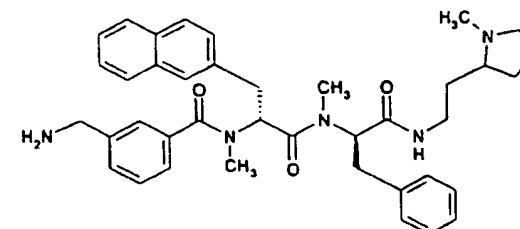
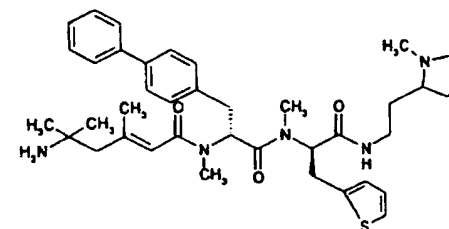
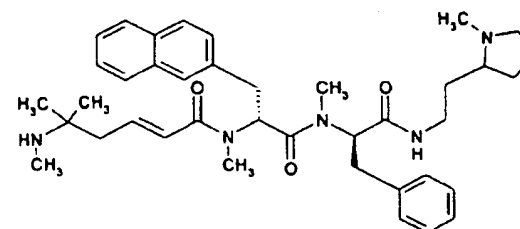
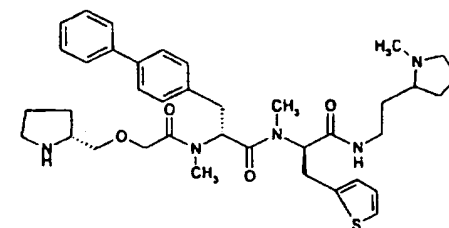
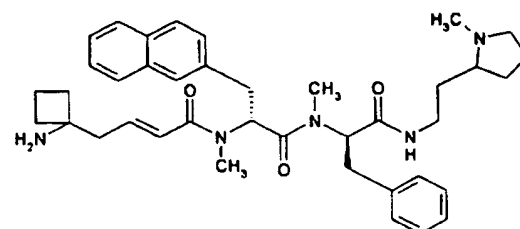
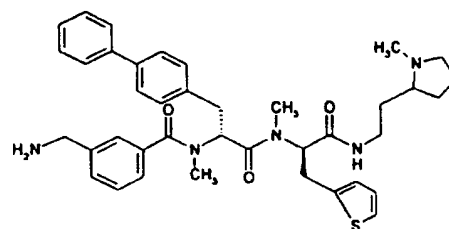
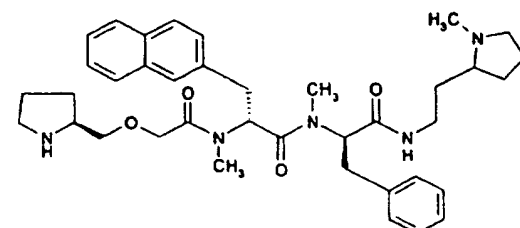
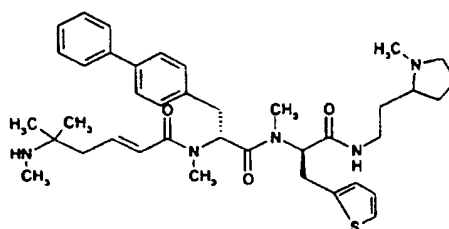
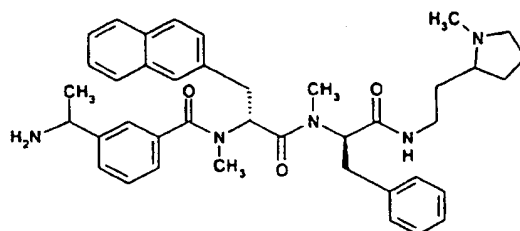
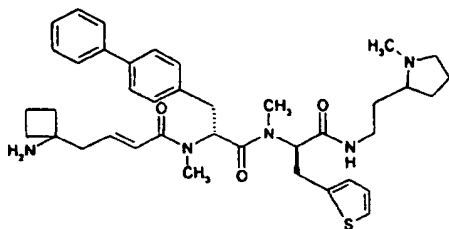


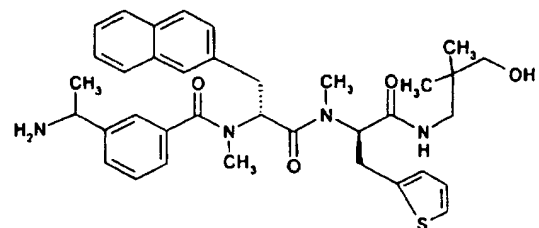
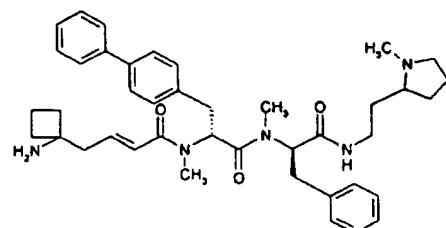
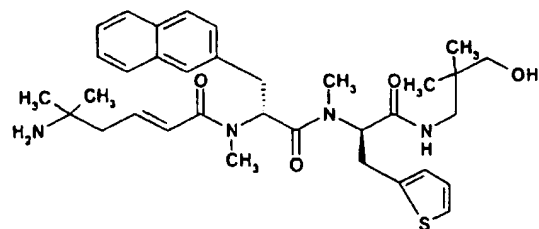
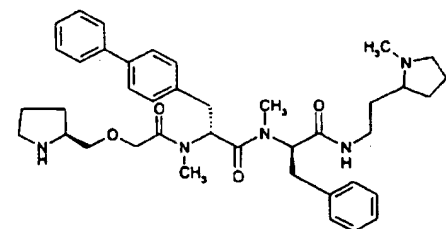
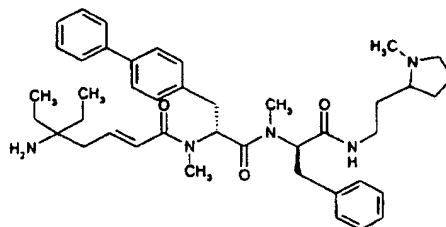
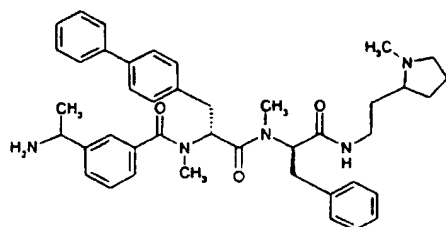
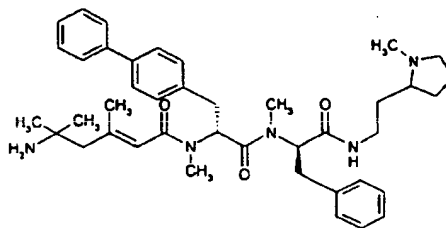
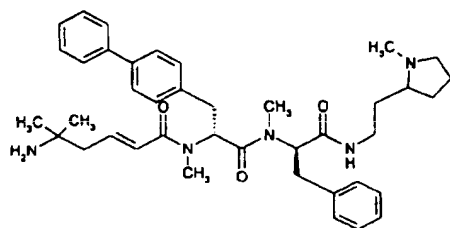
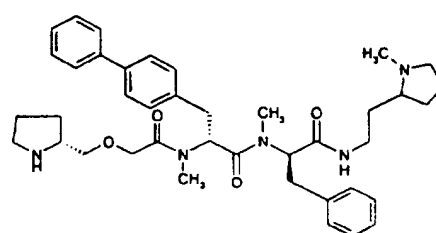
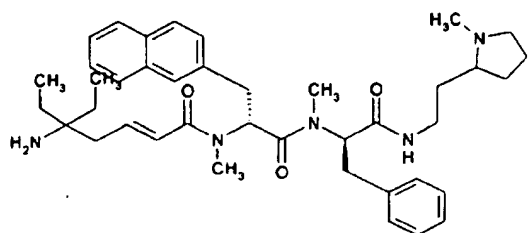
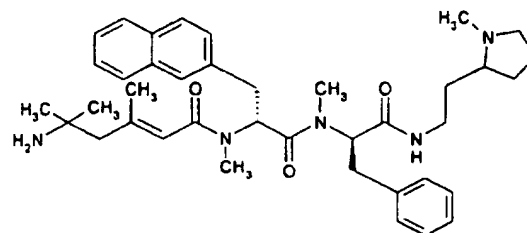
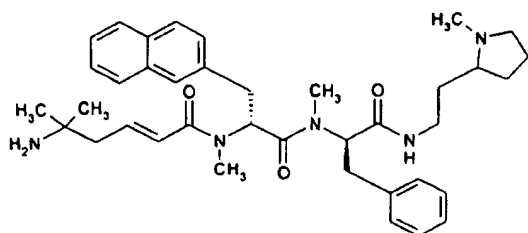


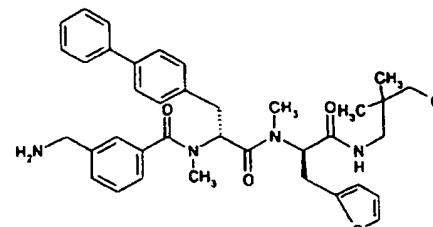
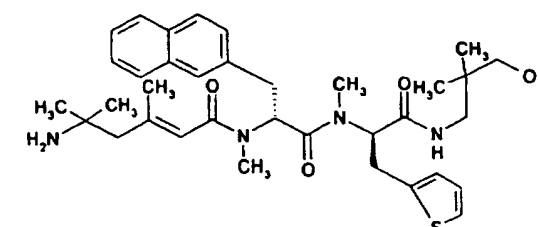
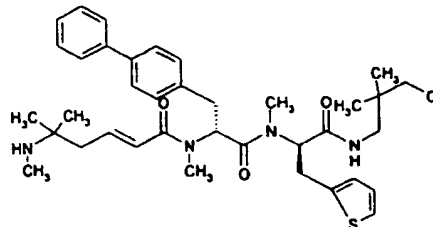
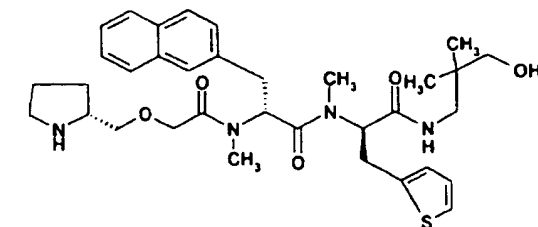
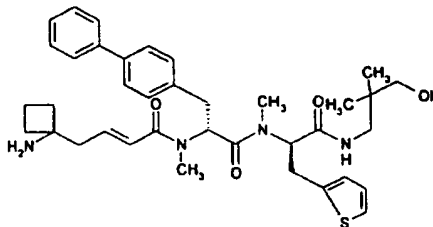
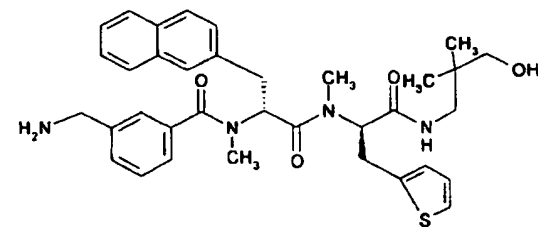
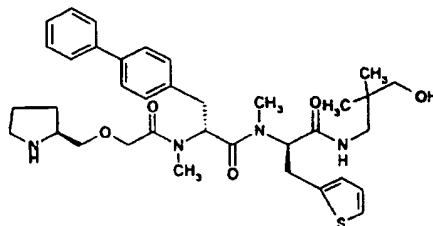
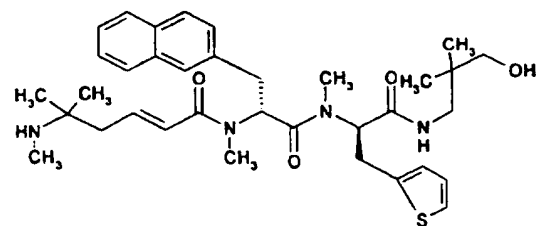
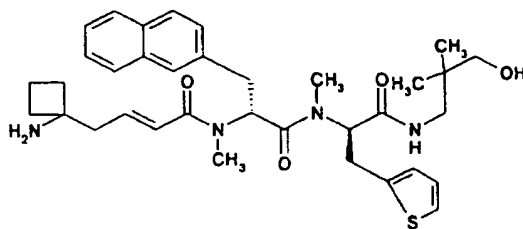
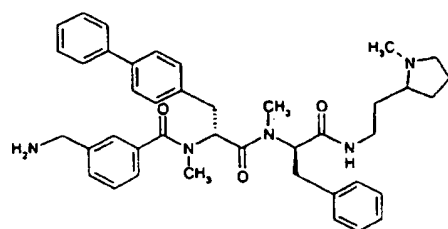
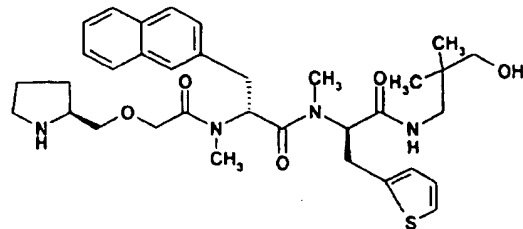
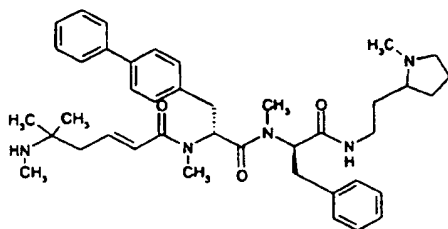


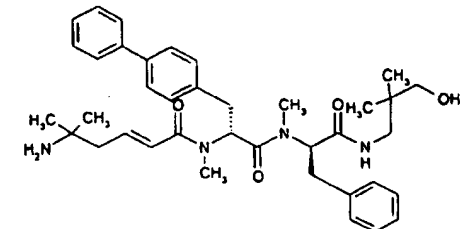
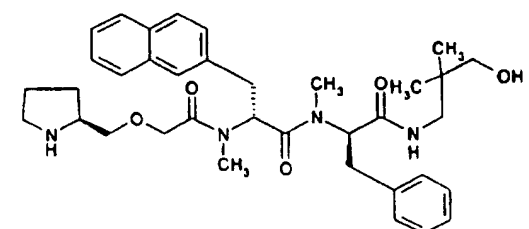
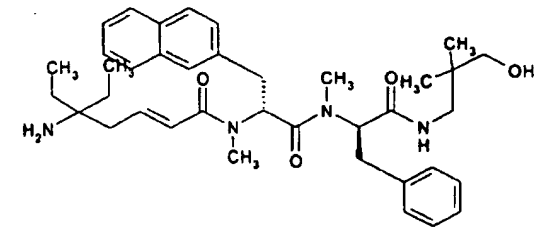
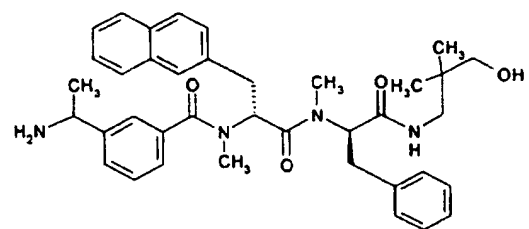
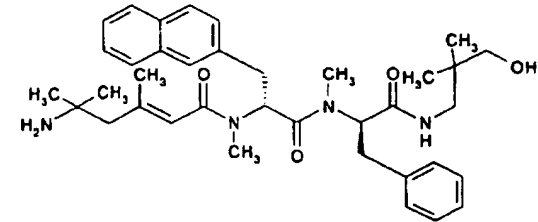
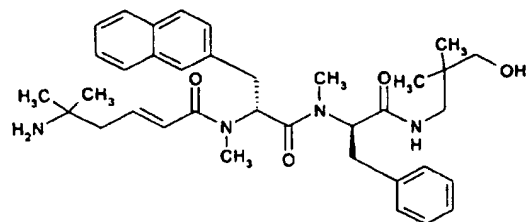
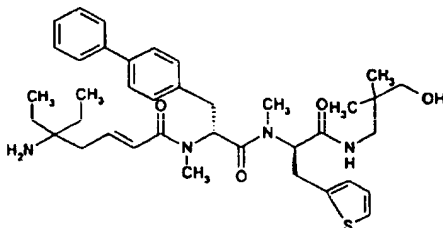
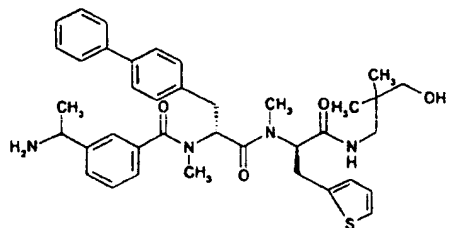
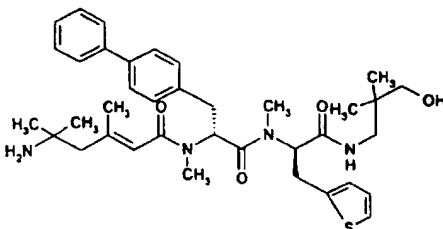
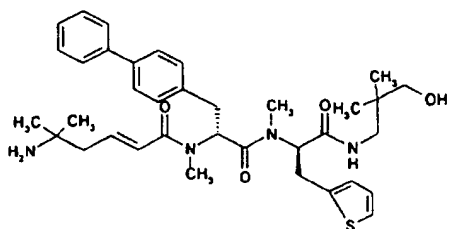
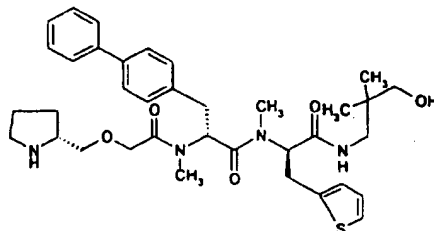
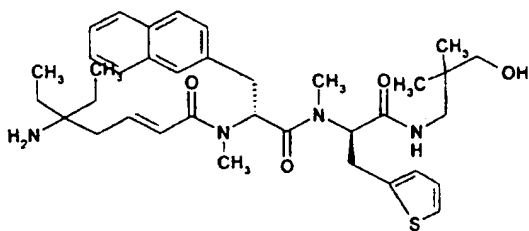


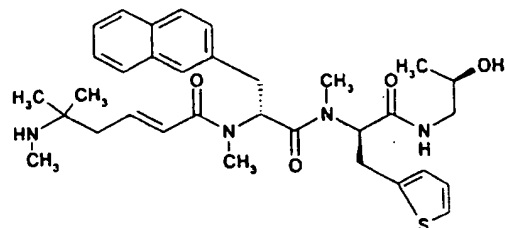
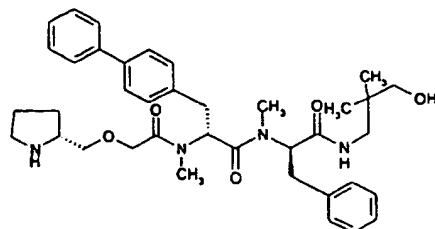
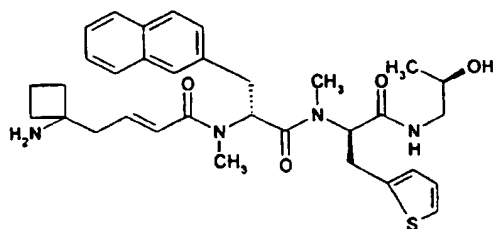
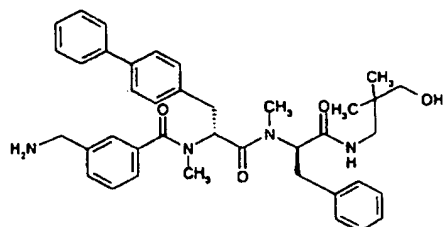
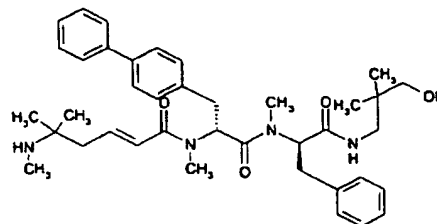
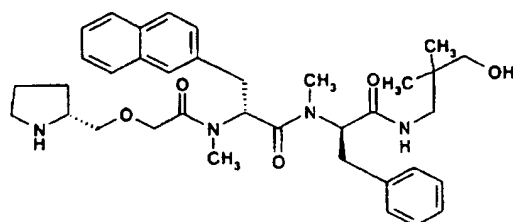
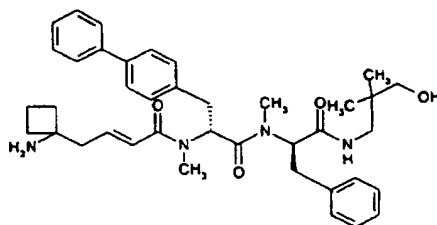
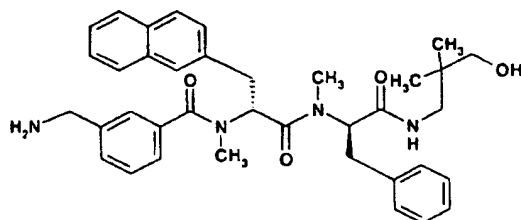
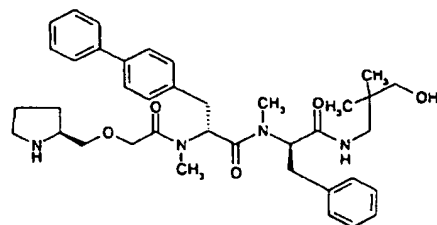
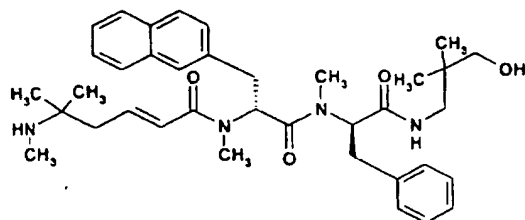
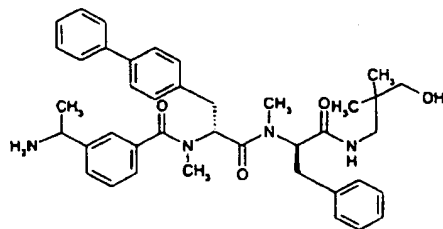
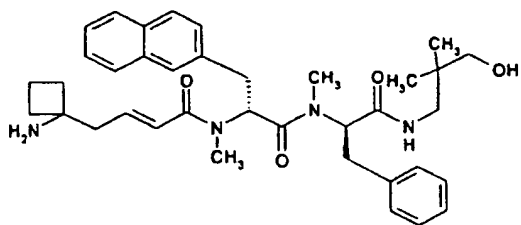


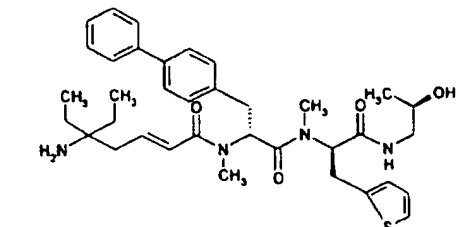
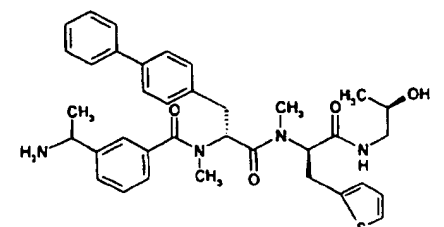
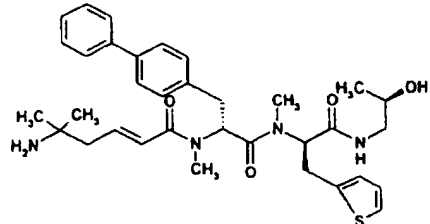
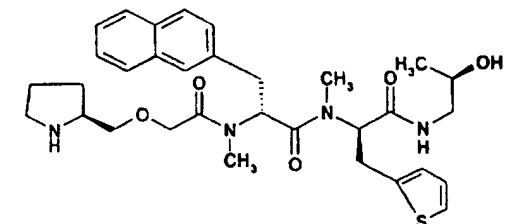
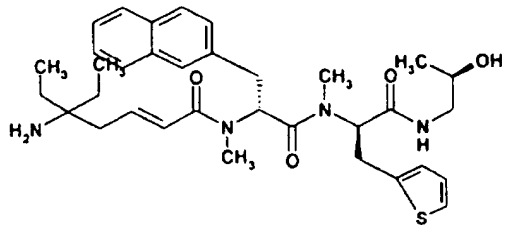
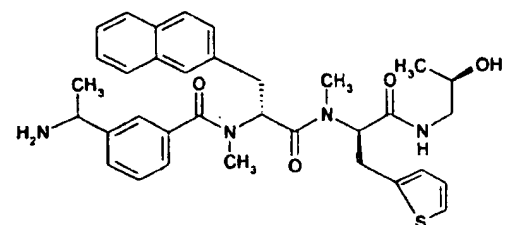
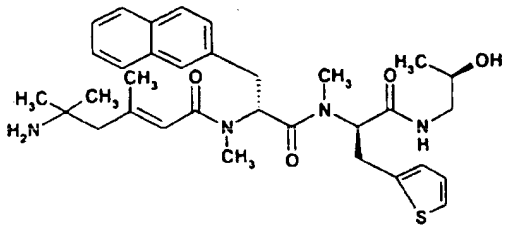
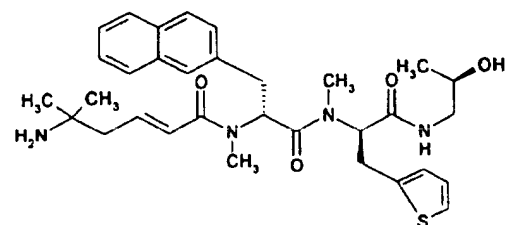
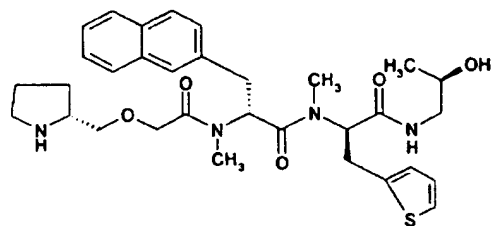
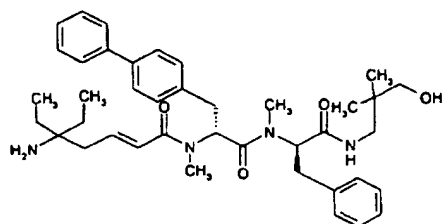
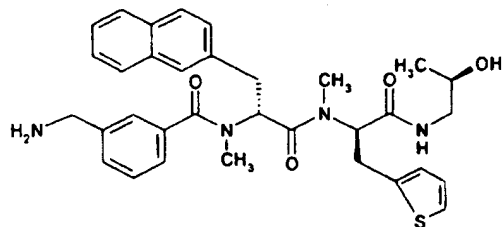
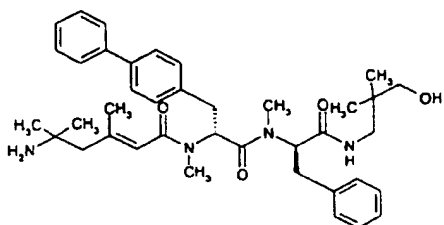


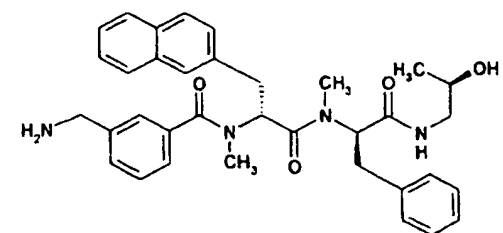
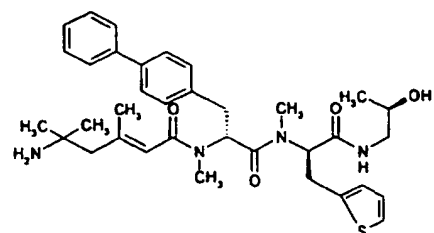
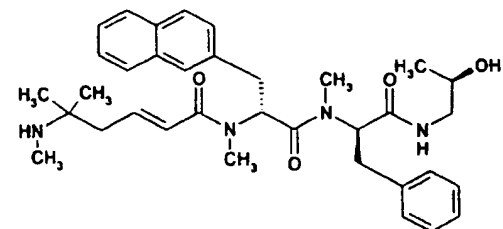
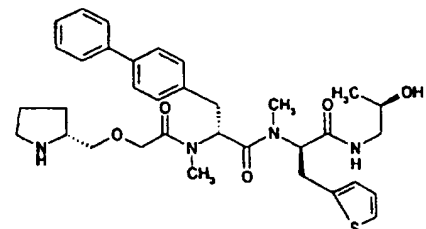
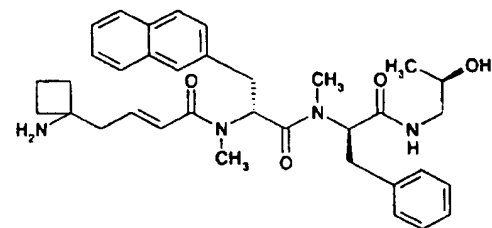
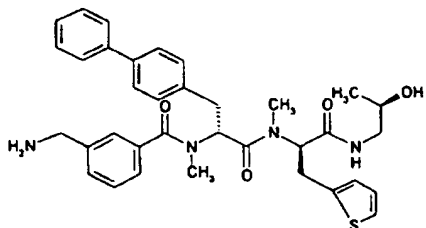
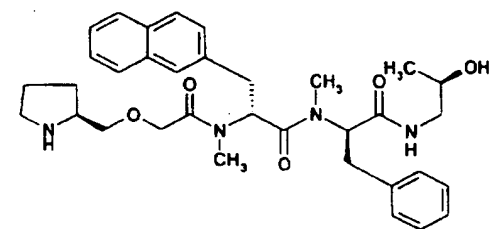
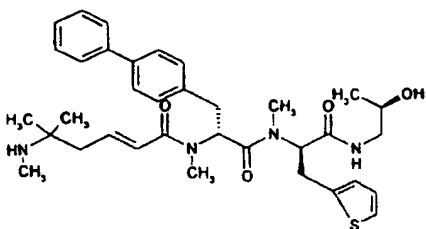
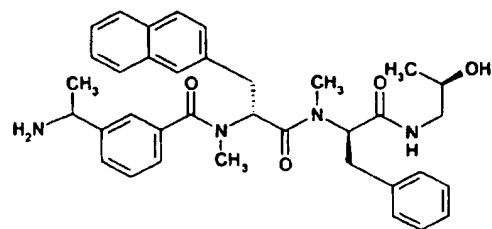
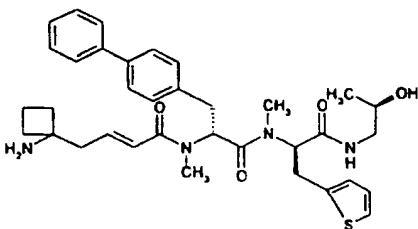
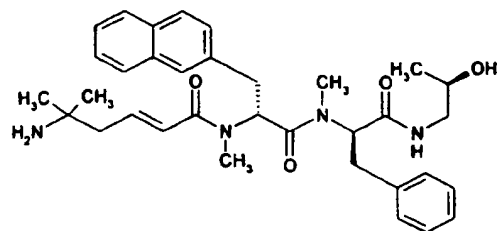
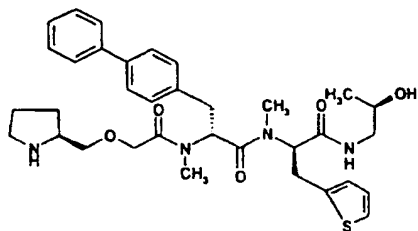


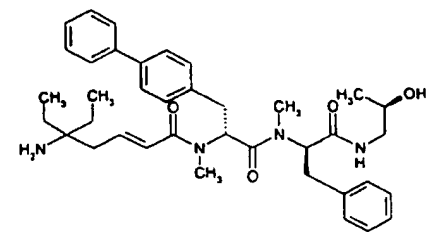
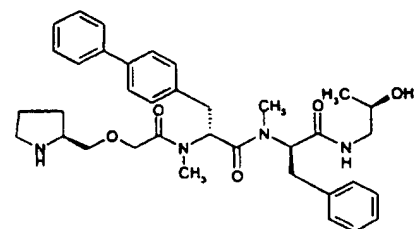
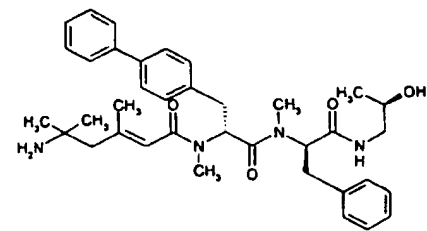
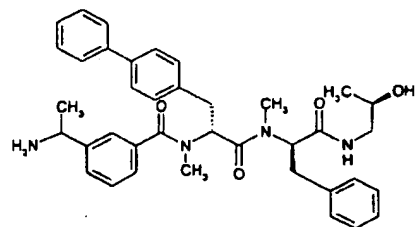
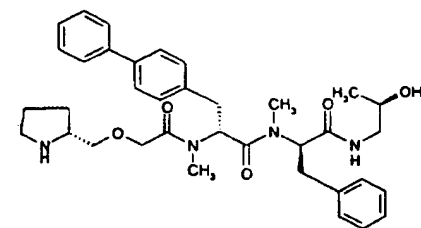
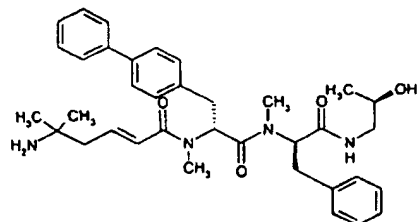
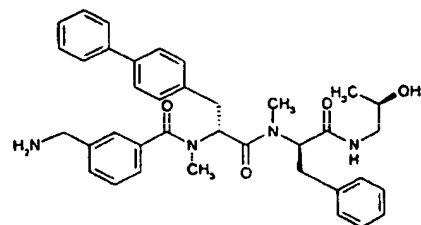
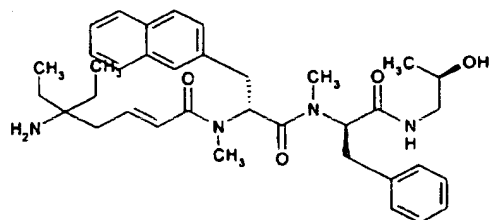
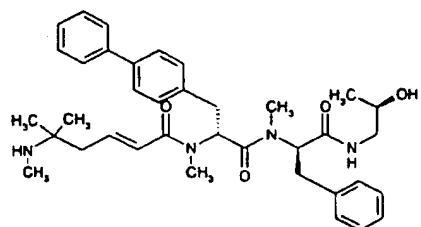
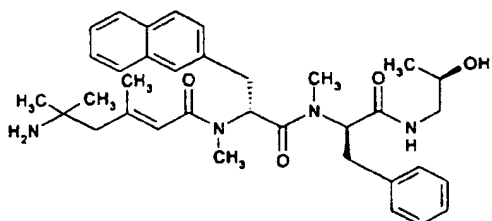
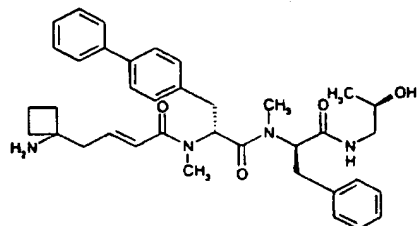
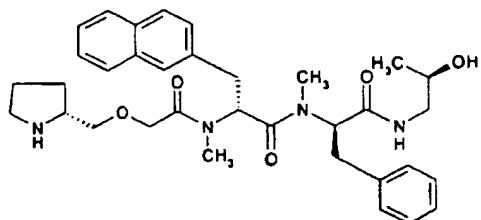












12. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

13. A composition according to claim 12 in unit dosage form, comprising from about 10 to about 200 mg of the compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof.

10

14. A pharmaceutical composition for stimulating the release of growth hormone from the pituitary, the composition comprising, as an active ingredient, a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

15

15. A pharmaceutical composition according to any one of the claims 12-14 for oral, nasal, transdermal, pulmonal, or parenteral administration.

16. A method of stimulating the release of growth hormone from the pituitary, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceeding composition claims .

25

17. A method of increasing the rate and extent of growth, the milk and wool production, or for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceeding composition claims.

30

18. The method according to claim 16 or 17, wherein the effective amount of the compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about
5 0.0001 to about 100 mg/kg body weight per day, preferably from about 0.001 to about 50 mg/kg body weight per day.

19. The method according to any one of the claims 16-18, wherein said administration is carried out by the oral, nasal, transdermal, pulmonal, or parenteral
10 route.

20. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

15

21. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for stimulating the release of growth hormone from the pituitary.

20 22. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for administration to animals to increase their rate and extent of growth, to increase their milk and wool production, or for the treatment of ailments.

25 23. Use of a compound according to any one of the preceeding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of stimulation of growth hormone release in the elderly; prevention of catabolic side effects of glucocorticoids, prevention and treatment of osteoporosis, stimulation of the immune system, acceleration of wound healing,
30 accelerating bone fracture repair, treatment of growth retardation, treating renal failure or insufficiency resulting from growth retardation, treatment of physiological short stature including growth hormone deficient children and short stature

associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal
5 dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients, treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation, treatment of pulmonary dysfunction and ventilator dependency, attenuation of
10 protein catabolic responses after major surgery, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis, adjuvant treatment for ovulation induction; to stimulate thymic development and prevent the age-related decline of thymic function, treatment of immunosuppressed patients, improvement in muscle strength, mobility,
15 maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly, stimulation of osteoblasts, bone remodelling and cartilage growth, stimulation of the immune system in companion animals and treatment of disorder of aging in companion animals, growth promoter in livestock and stimulation of wool growth in sheep.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 96/00529

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: C07K 14/60, C07K 5/10, C07K 7/02, A61K 38/07, A61K 38/08 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
REG, CAPLUS, DPCI		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9407519 A1 (SMITH-KLINE BEECHAM CORPORATION), 14 April 1994 (14.04.94) --	1-15,20-23
X	WO 9517423 A1 (NOVO NORDISK A/S), 29 June 1995 (29.06.95) --	1-15,20-23
P,X	WO 9615148 A2 (GENENTECH, INC.), 23 May 1996 (23.05.96) --	1-15,20-23
P,X	WO 9622997 A1 (NOVO NORDISK A/S), 1 August 1996 (01.08.96) -- -----	1-15,20-23
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
12 March 1997		09 -04- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Carolina Gómez Lagerlöf Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK96/00529

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-19
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☒ Claims Nos.: 1-9
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The formulation of claims 1-9 is so complicated because of the long lists of cascading substituents that it does not comply with Article 6 PCT prescribing that claims shall be clear and concise. For this reason the search has been mainly limited to the examples.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/97

International application No.

PCT/DK 96/00529

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 9407519	14/04/94	EP-A- 0663834 JP-T- 8502250	26/07/95 12/03/96
WO-A1- 9517423	29/06/95	AU-A- 1272495 CA-A- 2179597 EP-A- 0736039 FI-A- 962584 HU-A- 73497 HU-D- 9501947 IL-D- 112112 NO-A- 962665 PL-A- 315113 ZA-A- 9410261	10/07/95 29/06/95 09/10/96 20/06/96 28/08/96 00/00/00 00/00/00 23/08/96 14/10/96 23/06/95
WO-A2- 9615148	23/05/96	AU-A- 4164496 IL-D- 115994	06/06/96 00/00/00
WO-A1- 9622997	01/08/96	AU-A- 4431596 IL-D- 116923	14/08/96 00/00/00



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/06, C07D 471/04, 521/00, A61K 38/05, 31/395		A1	(11) International Publication Number: WO 97/24369
			(43) International Publication Date: 10 July 1997 (10.07.97)
(21) International Application Number: PCT/IB96/01353 (22) International Filing Date: 4 December 1996 (04.12.96) (30) Priority Data: 60/009,469 28 December 1995 (28.12.95) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CARPINO, Philip, A. [US/US]; 50 Meridian Street #2, Groton, CT 06340 (US). JARDINE, DaSilva, Paul, A. [GY/US]; 89 Angell Street, Providence, RI 02906 (US). LEFKER, Bruce, A. [US/US]; 21 Eagle Ridge Drive, Gales Ferry, CT 06335 (US). RAGAN, John, A. [US/US]; 1 Lark Lane, Gales Ferry, CT 06335 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		(81) Designated States: AU, BG, BR, BY, CA, CN, CZ, HU, IL, IS, JP, KR, KZ, LK, LV, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: GROWTH-HORMONE SECRETAGOGUES <div style="text-align: center;"> </div>			
(57) Abstract <p>This invention is directed to compounds of formula (I) and the pharmaceutically-acceptable salts thereof, where the substituents are as defined in the Specification, which are growth hormone secretagogues and which increase the level of endogenous growth hormone. The compounds of this invention are useful for the treatment and prevention of osteoporosis, congestive heart failure, frailty associated with aging, obesity; accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery; improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis. The compounds of the present invention are also useful in treating osteoporosis when used in combination with: a bisphosphonate compound such as alendronate; estrogen, premarin, and optionally progesterone; an estrogen agonist or antagonist; or calcitonin, and pharmaceutical compositions useful therefor. Further, the present invention is directed to pharmaceutical compositions useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an effective amount of a compound of the present invention and a growth hormone secretagogue selected from GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 or B-HT920. The invention is also directed to intermediates useful in the preparation of compounds of formula (I).</p>			

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GA	Gabon			VN	Viet Nam

-1-

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GROWTH-HORMONE SECRETAGOGUES

This invention relates to dipeptide compounds which are growth hormone secretagogues and are useful for the treatment and prevention of osteoporosis.

Background of the Invention

10 Growth hormone (GH), which is secreted from the pituitary gland, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic process of the body:

1. Increased rate of protein synthesis in substantially all cells of the body;
- 15 2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

Deficiency in growth hormone results in a variety of medical disorders. In children, it causes dwarfism. In adults, the consequences of acquired GH deficiency 20 include profound reduction in lean body mass and concomitant increase in total body fat, particularly in the truncal region. Decreased skeletal and cardiac muscle mass and muscle strength lead to a significant reduction in exercise capacity. Bone density is also reduced. Administration of exogenous growth hormone has been shown to reverse many of the metabolic changes. Additional benefits of therapy 25 have included reduction in LDL cholesterol and improved psychological well-being.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering an agent which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be 30 administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in an expensive product, and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone (e.g., Jacob-Creutzfeld disease). Recently, recombinant growth hormone has become available which, while 35 no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Most GH deficiencies are caused by defects in GH release, not primary defects in pituitary synthesis of GH. Therefore, an alternative strategy for

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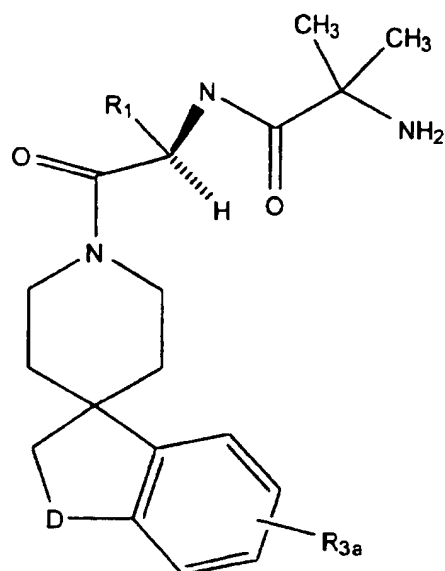
normalizing serum GH levels is by stimulating its release from somatotrophs. Increasing GH secretion can be achieved by stimulating or inhibiting various neurotransmitter systems in the brain and hypothalamus. As a result, the development of synthetic growth hormone-releasing agents to stimulate pituitary GH secretion are being pursued, and may have several advantages over expensive and inconvenient GH replacement therapy. By acting along physiologic regulatory pathways, the most desirable agents would stimulate pulsatile GH secretion, and excessive levels of GH that have been associated with the undesirable side effects of exogenous GH administration would be avoided by virtue of intact negative feedback loops.

Physiologic and pharmacologic stimulators of GH secretion include arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GHRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. WO 94/13696 refers to certain spiropiperidines and homologues which promote release of growth hormone. Preferred compounds are of the general structure shown below.

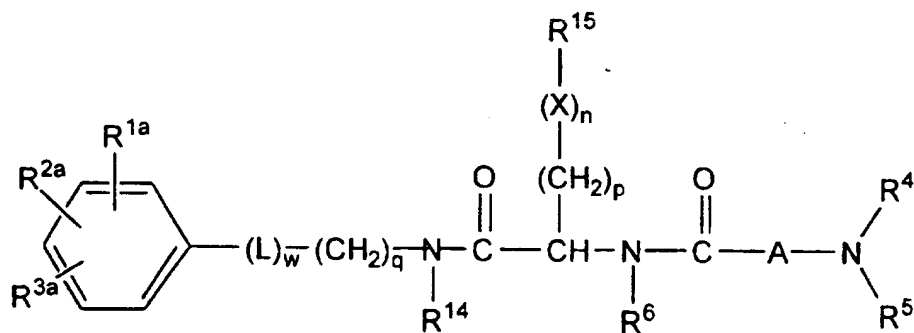
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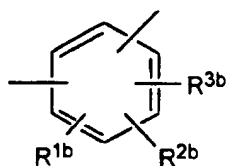


WO 94/11012 refers to certain dipeptides that promote release of growth hormone. These dipeptides have the general structure

5



where L is



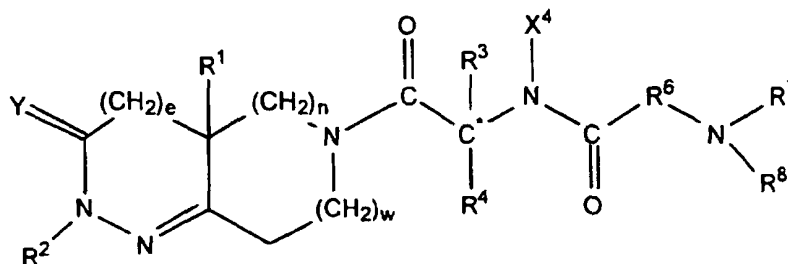
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The compounds of WO 94/11012 and WO 94/13696 are reported to be useful in the treatment of osteoporosis in combination with parathyroid hormone or a bisphosphonate.

Summary of the Invention

5 This invention provides compounds of the formula:



(I)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts and prodrugs thereof,

10 wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

- 15 R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_l-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_l-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_l-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_l-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_l-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_l-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_l-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_l-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_l-A^1$, $-(C_1-C_{10})alkyl$, $-(CH_2)_l-A^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$, $-(CH_2)_q-Y^1-(CH_2)_l-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_l-(C_3-C_7)cycloalkyl$;
- 20

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro; Y^1 is O, $S(O)_m$, $-C(O)NX^6-$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6-$, $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

25

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q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4) alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl,

5 $-CO_2(C_1-C_4)$ alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4) alkyl;

R^2 is hydrogen, (C_1-C_8) alkyl, $-(C_0-C_3)$ alkyl- (C_3-C_8) cycloalkyl, $-(C_1-C_4)$ alkyl- A^1 or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$,

10 $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;

R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl,

$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl, $-(C_1-C_5)$ alkyl- X^1 - (C_0-C_5) alkyl- A^1 or

$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl- (C_3-C_7) cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with, -

15 $S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,

$-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, $(C_5-$

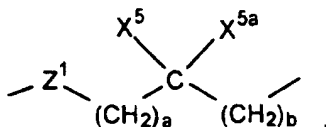
20 $C_7)$ cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having

1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or

fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms

25 independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



R^6 is a bond or is

30

where a and b are independently 0, 1, 2 or 3;

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X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is optionally substituted with a substituent selected from the group consisting of A^1 , OX^2 , $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R^7 and R^8 wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X^5 or X^{5a} but not both may be on the carbon atom and R^7 or R^8 but not both may be on the nitrogen atom and further provided that when two alkylene bridges are formed then X^5 and X^{5a} cannot be on the carbon atom and R^7 and R^8 cannot be on the nitrogen atom;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^7 and R^8 are independently hydrogen or optionally substituted (C_1-C_6) alkyl;

where the optionally substituted (C_1-C_6) alkyl in the definition of R^7 and R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or

R^7 and R^8 can be taken together to form $-(CH_2)_r-L-(CH_2)_r-$;

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where L is $C(X^2)(X^2)$, $S(O)_m$ or $N(X^2)$;

A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6) alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$ alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$ -phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl or tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6) alkoxycarbonyl, $-S(O)_m(C_1-C_6)$ alkyl 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10}) alkanoyloxy or 1 to 3 (C_1-C_6) alkoxy;

X^{12} is hydrogen, (C_1-C_6) alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3 , OCH_3 , OCF_3 and CF_3 ;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r-$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

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X^2 for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X^2 are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5
 5 halogens or 1 to 3 OX³;

X^3 for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X^6 is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the
 10 definition of X^6 is optionally independently substituted by 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, carboxylate (C₁-C₄)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the
 15 atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X^7 is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and

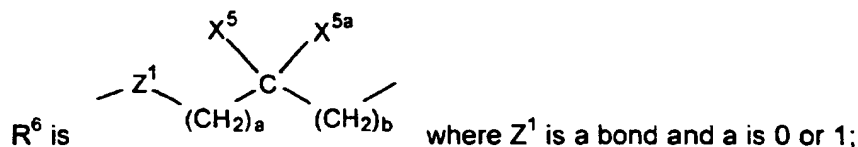
m for each occurrence is independently 0, 1 or 2;

with the proviso that:

20 X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²; and

when R⁶ is a bond then L is N(X²) and each r in the definition -(CH₂)_r-L-(CH₂)_r- is independently 2 or 3.

A preferred group of compounds, designated the "A Group", contains those
 25 compounds having the formula I as shown hereinabove wherein X⁴ is hydrogen; R⁴ is hydrogen or methyl; R⁷ is hydrogen or (C₁-C₃)alkyl; R⁸ is hydrogen or (C₁-C₃)alkyl optionally substituted with one or two hydroxyl groups;



X^5 and X^{5a} are each independently hydrogen, trifluoromethyl, phenyl, optionally
 30 substituted (C₁-C₆)alkyl;

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where the optionally substituted (C₁-C₆)alkyl is optionally substituted with OX², imidazolyl, phenyl, indolyl, p-hydroxyphenyl, (C₅-C₇)cycloalkyl, -S(O)_m(C₁-C₆)alkyl, -N(X²)(X²) or -C(O)N(X²)(X²);

or X⁵ and R⁷ are taken together to form a (C₁-C₅)alkylene bridge, and the other
 5 substituents not defined for the "A Group" compounds are as defined for formula (I) hereinabove.

A group of compounds, which is preferred among the "A Group" of compounds, designated the "B Group", contains those compounds of the "A Group", having the formula I as shown hereinabove, wherein b is 0; X⁵ and X^{5a} are each
 10 independently hydrogen, (C₁-C₃)alkyl or hydroxy(C₁-C₃)alkyl; R³ is selected from the group consisting of 1-indolyl-CH₂-, 2-indolyl-CH₂-, 3-indolyl-CH₂-, 1-naphthyl-CH₂-, 2-naphthyl-CH₂-, 1-benzimidazolyl-CH₂-, 2-benzimidazolyl-CH₂-, phenyl-(C₁-C₄)alkyl-, 2-pyridyl-(C₁-C₄)alkyl-, 3-pyridyl-(C₁-C₄)alkyl-, 4-pyridyl-(C₁-C₄)alkyl-, phenyl-CH₂-S-CH₂-, thienyl-(C₁-C₄)alkyl-, phenyl-(C₀-C₃)alkyl-O-CH₂-, phenyl-CH₂-O-phenyl-CH₂-,
 15 and 3-benzothieryl-CH₂-;

where the aryl portion(s) of the groups defined for R³ are optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH₃, OCH₃, OCF₃, OCF₂H and CF₃.

20 A group of compounds, which is preferred among the "B Group" of compounds, designated the "C Group", contain those compounds of the "B Group", having the formula I as shown hereinabove, wherein R⁴ is hydrogen; a is 0; n is 1 or 2; w is 0 or 1; X⁵ and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X⁵ is hydrogen then X^{5a} is not hydrogen;

25 R⁷ and R⁸ are each hydrogen; and

R³ is phenyl-CH₂-O-CH₂-, phenyl-CH₂-S-CH₂-, 1-naphthyl-CH₂-, 2-naphthyl-CH₂-, phenyl-(CH₂)₃- or 3-indolyl-CH₂-;

where the aryl portion of the groups defined for R³ is optionally substituted with one to three substituents, each substituent being independently selected
 30 from the group consisting of fluoro, chloro, methyl, OCH₃, OCF₂H, OCF₃ and CF₃.

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A group of compounds, which is preferred among the "C Group" of compounds, designated the "D Group", contains those compounds of the "C Group", having the formula I as shown hereinabove, wherein R^1 is $-(CH_2)_t-A^1$,

$-(CH_2)_q-(C_3-C_7)\text{cycloalkyl}$ or $(C_1-C_{10})\text{alkyl}$;

- 5 where A^1 in the definition of R^1 is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of fluoro, chloro, methyl, OCH_3 , OCF_2H , OCF_3 and CF_3 ;

the cycloalkyl and alkyl groups in the definition of R^1 are optionally substituted with $(C_1-C_4)\text{alkyl}$, hydroxyl, $(C_1-C_4)\text{alkoxy}$, carboxyl, $CONH_2$,

- 10 $-S(O)_m(C_1-C_6)\text{alkyl}$, $-CO_2(C_1-C_4)\text{alkyl ester}$, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y is O; R^2 is hydrogen, $-(C_0-C_3)\text{alkyl}$ -(C_3-C_8)cycloalkyl, phenyl or $(C_1-C_8)\text{alkyl}$ where the $(C_1-C_8)\text{alkyl}$ group is optionally substituted with hydroxyl, $-CF_3$ or 1 to 3 halogen.

A group of compounds, which is preferred among the "D Group" of compounds, designated the "E Group", contains those compounds of the "D Group"

- 15 wherein w is 0 and n is 1.

Another group of compounds, which is preferred among the "D Group" of compounds, designated the "F Group", are those compounds of the "D Group", having the formula I as shown hereinabove, wherein e is 0; n and w are each 1;

R^1 is $-(CH_2)_t-A^1$;

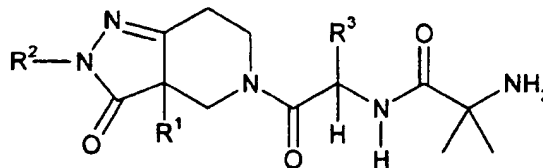
- 20 where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ;

t is 0, 1 or 2;

- 25 and R^3 is phenyl- CH_2-O-CH_2- , phenyl- $(CH_2)_3-$ or 3-indolyl- CH_2- , where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 or OCF_2H .

- 30 A group of compounds, which is preferred among the "F Group" of compounds, designated the "G Group", contains those compounds of the "F Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^1 is $-CH_2\text{-phenyl}$, $-CH_2\text{-4-fluoro-phenyl}$, $-CH_2\text{-pyridyl}$ or $-CH_2\text{-thiazolyl}$ and R^2 is hydrogen, methyl, ethyl, t-butyl or $-CH_2CF_3$.

A group of compounds, which is preferred among the "G Group" of compounds, designated the "G¹ Group", contains those compounds of the "G Group", and have the formula



- 5 the racemic-diastereomeric mixtures and optical isomers of said compounds wherein
 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is $-(\text{CH}_2)_3\text{-phenyl}$;
 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is 3-indolyl- $\text{CH}_2\text{-}$;
 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is ethyl and R^3 is 3-indolyl- $\text{CH}_2\text{-}$;
 R^1 is $-\text{CH}_2\text{-4-fluoro-phenyl}$, R^2 is methyl and R^3 is 3-indolyl- $\text{CH}_2\text{-}$;
- 10 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is ethyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is $-\text{CH}_2\text{-CF}_3$ and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
 R^1 is $-\text{CH}_2\text{-4-fluoro-phenyl}$, R^2 is methyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is t-butyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$; or
- 15 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-3,4-di-fluoro-phenyl}$.

- 20 The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(3,4-difluoro-benzyl-oxymethyl)-2-oxo-ethyl]-2-methyl-propionamide is preferred among the "G¹ Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds, which is preferred among the "G Group" of compounds, designated the "H Group", contains those compounds of the "G Group", having the formula I as shown hereinabove, wherein R^1 is $-\text{CH}_2\text{-phenyl}$ and R^3 is phenyl- $(\text{CH}_2)_3\text{-}$.

- 25 The diastereomeric mixture of 2-amino-N-[1-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide is preferred among the "H Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

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A group of compounds, which is preferred among the "G Group" of compounds, designated the "I Group", contains those compounds of the "G Group" wherein R¹ is -CH₂-phenyl or -CH₂-4-fluoro-phenyl and R³ is 3-indolyl-CH₂-.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide is preferred among the "I Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide is also preferred among the "I Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide is also preferred among the "I Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds which is preferred among the "G Group" of compounds, designated the "J Group", contains those compounds of the "G Group" wherein R¹ is -CH₂-phenyl or -CH₂-4-fluoro-phenyl and R³ is phenyl-CH₂-O-CH₂-.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is preferred among the "J Group" of compounds, the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture, the 3a-(R) isomer is preferred over the 3a-(S) isomer, and the L-tartaric acid salt of the 3a-(R) isomer is a preferred salt.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is also preferred among the "J Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-[3a-(R,S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is also preferred among the "J Group"

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of compounds, the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture and the 3a-(R) isomer is preferred over the 3a-(S) isomer.

The diastereomeric mixture of 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide is also preferred among the "J Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is also preferred among the "J Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

A group of compounds which is preferred among the "D Group" of compounds, designated the "K Group", contains those compounds of the "D Group" wherein e is 1; n is 1; w is 1; R¹ is -(CH₂)_t-A¹;

where A¹ in the definition of R¹ is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H;

t is 0, 1 or 2;

and R³ is phenyl-CH₂-O-CH₂-, phenyl-(CH₂)₃- or 3-indolyl-CH₂-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ or OCF₂H.

A group of compounds which is preferred among the "K Group" of compounds, designated the "L Group", are those compounds of the "K Group" wherein X⁵ and X^{5a} are each methyl; R¹ is -CH₂-phenyl, -CH₂-4-fluoro-phenyl, -CH₂-pyridyl or -CH₂-thiazolyl and R² is hydrogen, methyl, ethyl, t-butyl or -CH₂CF₃.

A group of compounds which is preferred among the "L Group", designated the "L¹ Group", are those compounds of the "L Group" wherein R¹ is -CH₂-phenyl; R² is hydrogen or methyl and R³ is -CH₂-O-CH₂-phenyl.

The diastereomeric mixture of 2-amino-N-[2-(3a-(R,S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide is preferred among the "J Group", the separated 3a-(R) and 3a-

(S) isomers are preferred of the diastereomeric mixture and the 3a-(R) isomer is preferred over the 3a-(S) isomer.

Another group of compounds, which is preferred among the "A Group" of compounds, designated the "M Group", contains those compounds of the "A Group",
 5 having the formula I as shown hereinabove, wherein b is 0; X^5 and X^{5a} are each independently hydrogen, (C₁-C₃)alkyl or hydroxy(C₁-C₃)alkyl;
 R^3 is selected from the group consisting of 1-indolyl-CH₂-, 2-indolyl-CH₂-, 3-indolyl-CH₂-, 1-naphthyl-CH₂-, 2-naphthyl-CH₂-, 1-benzimidazolyl-CH₂-, 2-benzimidazolyl-CH₂-, phenyl-(C₁-C₄)alkyl-, 2-pyridyl-(C₁-C₄)alkyl-, 3-pyridyl-(C₁-C₄)alkyl-, 4-pyridyl-
 10 (C₁-C₄)alkyl-, phenyl-CH₂-S-CH₂-, thienyl-(C₁-C₄)alkyl-, phenyl-(C₀-C₃)alkyl-O-CH₂-, phenyl-CH₂-O-phenyl-CH₂-, 3-benzothieryl-CH₂-, thienyl-CH₂-O-CH₂-, thiazolyl-CH₂-O-CH₂-, pyridyl-CH₂-O-CH₂-, pyrimidyl-CH₂-O-CH₂- and phenyl-O-CH₂-CH₂;

where the aryl portion(s) of the groups defined for R^3 are optionally substituted with one to three substituents, each substituent being
 15 independently selected from the group consisting of methylenedioxy, F, Cl, CH₃, OCH₃, OCF₃, OCF₂H and CF₃.

A group of compounds, which is preferred among the "M Group" of compounds, designated the " M^1 Group", contains those compounds of the "M Group", having the formula I as shown hereinabove, wherein R^4 is hydrogen; a is 0;
 20 n is 1; w is 1; e is 0; X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen; R^7 and R^8 are each hydrogen; Y is oxygen; R^2 is hydrogen, methyl, ethyl, propyl, i-propyl, t-butyl, -CH₂CF₃, CF₃ or -CH₂-cyclopropyl; R^1 is CH₂-A¹; where A¹ in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with
 25 one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H; and R^3 is phenyl-CH₂-O-CH₂-, phenyl-(CH₂)₃-, 3-indolyl-CH₂-, thienyl-CH₂-O-CH₂-, thiazolyl-CH₂-O-CH₂-, pyridyl-CH₂-O-CH₂-, pyrimidyl-CH₂-O-CH₂- or phenyl-O-CH₂-CH₂-, where the aryl portion is optionally substituted with one to three substituents, each substituent being
 30 independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H.

A group of compounds, which is preferred among the " M^1 Group" of compounds, designated the "N Group", contains those compounds of the " M^1

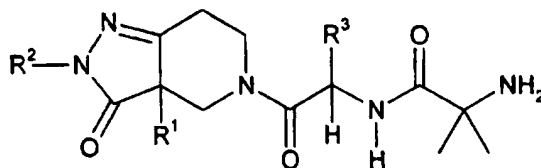
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Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or $-\text{CH}_2\text{CF}_3$; A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ; R^3 is phenyl- CH_2 -O- CH_2 -,
 5 phenyl- $(\text{CH}_2)_3$ - or thienyl- CH_2 -O- CH_2 - where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H .

Another group of compounds, which is preferred among the " M^1 Group" of compounds, designated the "O Group", contains those compounds of the " M^1
 10 Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH_2CF_3 ; A^1 is 2-pyridyl or 3-pyridyl optionally substituted with one to two substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ; R^3 is phenyl- CH_2 -O- CH_2 -, phenyl- $(\text{CH}_2)_3$ - or thienyl- CH_2 -O- CH_2 - where the aryl portion is
 15 optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H .

Another group of compounds, which is preferred among the " M^1 Group" of compounds, designated the "P Group", contains those compounds of the " M^1
 20 Group", having the formula I as shown hereinabove, wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH_2CF_3 ; A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ; R^3 is 2-pyridyl- CH_2 -O- CH_2 -, or 3-pyridyl- CH_2 -O- CH_2 - where the aryl portion is optionally substituted with one to two
 25 substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H .

A group of compounds, which is preferred among the "O Group" of compounds, designated the "Q Group", contains those compounds of the "O Group", having the formula



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the racemic-diastereomeric mixtures and optical isomers of said compounds wherein R^2 is methyl; A^1 is 2-pyridyl; and R^3 is $-\text{CH}_2-\text{O}-\text{CH}_2$ -phenyl;

R^2 is CH_2CF_3 ; A^1 is 2-pyridyl; and R^3 is $-\text{CH}_2-\text{O}-\text{CH}_2$ -3-chloro-phenyl;

R^2 is CH_2CF_3 ; A^1 is 2-pyridyl; and R^3 is $-\text{CH}_2-\text{O}-\text{CH}_2$ -4-chloro-phenyl;

5 R^2 is CH_2CF_3 ; A^1 is 2-pyridyl; and R^3 is $-\text{CH}_2-\text{O}-\text{CH}_2$ -2,4-di-chloro-phenyl;

R^2 is CH_2CF_3 ; A^1 is 2-pyridyl; and R^3 is $-\text{CH}_2-\text{O}-\text{CH}_2$ -3-chloro-thiophene; or

R^2 is CH_2CF_3 ; A^1 is 2-pyridyl; and R^3 is $-\text{CH}_2-\text{O}-\text{CH}_2$ -2,4-di-fluoro-phenyl.

The diastereomeric mixture of 2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-
10 c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[1-(R)-(3-chloro-benzyloxy-methyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-
15 hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl]-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[1-(R)-(4-chloro-benzyloxy-methyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-
20 hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl]-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-
25 2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl]-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

The diastereomeric mixture of 2-amino-N-[1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-
30 2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl]-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

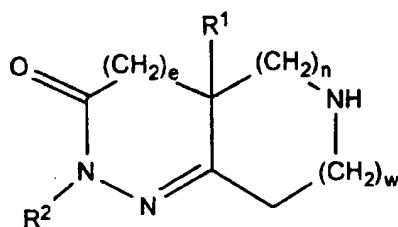
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The diastereomeric mixture of 2-amino-N-{1-(R)-(2,4-difluoro-benzyloxy-methyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-

2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl)-2-methyl-propionamide is preferred among the "Q Group" of compounds and the separated 3a-(R) and 3a-(S)

5 isomers are preferred of the diastereomeric mixture.

A group of compounds which contains intermediates useful in synthesizing the compounds of formula (I) are of the formula



(II)

10 the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts thereof, wherein e is 0 or 1; n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

R¹ is hydrogen, -CN, -(CH₂)ᵩN(X⁶)C(O)X⁶, -(CH₂)ᵩN(X⁶)C(O)(CH₂)ᵩ-A¹,

-(CH₂)ᵩN(X⁶)SO₂(CH₂)ᵩ-A¹, -(CH₂)ᵩN(X⁶)SO₂X⁶, -(CH₂)ᵩN(X⁶)C(O)N(X⁶)(CH₂)ᵩ-A¹,

15 -(CH₂)ᵩN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)ᵩC(O)N(X⁶)(X⁶), -(CH₂)ᵩC(O)N(X⁶)(CH₂)ᵩ-A¹,

-(CH₂)ᵩC(O)OX⁶, -(CH₂)ᵩC(O)O(CH₂)ᵩ-A¹, -(CH₂)ᵩOX⁶, -(CH₂)ᵩOC(O)X⁶,

-(CH₂)ᵩOC(O)(CH₂)ᵩ-A¹, -(CH₂)ᵩOC(O)N(X⁶)(CH₂)ᵩ-A¹, -(CH₂)ᵩOC(O)N(X⁶)(X⁶),

-(CH₂)ᵩC(O)X⁶, -(CH₂)ᵩC(O)(CH₂)ᵩ-A¹, -(CH₂)ᵩN(X⁶)C(O)OX⁶,

-(CH₂)ᵩN(X⁶)SO₂N(X⁶)(X⁶), -(CH₂)ᵩS(O)ₘX⁶, -(CH₂)ᵩS(O)ₘ(CH₂)ᵩ-A¹,

20 -(C₁-C₁₀)alkyl, -(CH₂)ᵩ-A¹, -(CH₂)ᵩ-(C₃-C₇)cycloalkyl, -(CH₂)ᵩ-Y¹-(C₁-C₆)alkyl,

-(CH₂)ᵩ-Y¹-(CH₂)ᵩ-A¹ or -(CH₂)ᵩ-Y¹-(CH₂)ᵩ-(C₃-C₇)cycloalkyl;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂,

-S(O)ₘ(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl or 1 to 3 fluoro; Y¹ is O,

25 S(O)ₘ, -C(O)NX⁶, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-, -C(O)O-,

-OC(O)N(X⁶)- or -OC(O)-; q is 0, 1, 2, 3 or 4; t is 0, 1, 2 or 3;

said (CH₂)ᵩ group and (CH₂)ᵩ group may each be optionally substituted with 1 to 3 fluoro, 1 or 2 (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

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$-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{CO}_2(\text{C}_1-\text{C}_4)\text{alkyl ester}$, or 1H-tetrazol-5-yl;

R^2 is hydrogen, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $-(\text{C}_0-\text{C}_3)\text{alkyl}-(\text{C}_3-\text{C}_8)\text{cycloalkyl}$, $-(\text{C}_1-\text{C}_4)\text{alkyl}-\text{A}^1$ or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted by hydroxyl, $-\text{C}(\text{O})\text{OX}^6$, $-\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{N}(\text{X}^6)(\text{X}^6)$,

5 $-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{A}^1$, $-\text{C}(\text{O})(\text{X}^6)$, CF_3 , CN or 1 to 3 halogen;

A^1 for each occurrence is independently $(\text{C}_5-\text{C}_7)\text{cycloalkenyl}$, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

15 A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-\text{OX}^6$, $-\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{C}(\text{O})\text{OX}^6$, oxo, $(\text{C}_1-\text{C}_6)\text{alkyl}$, nitro, cyano, benzyl, $-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{N}(\text{X}^6)\text{C}(\text{O})(\text{X}^6)$, $-\text{SO}_2\text{N}(\text{X}^6)(\text{X}^6)$, $-\text{N}(\text{X}^6)\text{SO}_2\text{-phenyl}$, $-\text{N}(\text{X}^6)\text{SO}_2\text{X}^6$, $-\text{CONX}^{11}\text{X}^{12}$, $-\text{SO}_2\text{NX}^{11}\text{X}^{12}$, $-\text{NX}^6\text{SO}_2\text{X}^{12}$, $-\text{NX}^6\text{CONX}^{11}\text{X}^{12}$, $-\text{NX}^6\text{SO}_2\text{NX}^{11}\text{X}^{12}$, $-\text{NX}^6\text{C}(\text{O})\text{X}^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted by one methylenedioxy;

where X^{11} is hydrogen or optionally substituted $(\text{C}_1-\text{C}_6)\text{alkyl}$;

the optionally substituted $(\text{C}_1-\text{C}_6)\text{alkyl}$ defined for X^{11} is optionally independently substituted with phenyl, phenoxy, $(\text{C}_1-\text{C}_6)\text{alkoxycarbonyl}$, $-\text{S}(\text{O})_m(\text{C}_1-\text{C}_6)\text{alkyl}$, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $(\text{C}_1-\text{C}_{10})\text{alkanoyloxy}$ or 1 to 3 $(\text{C}_1-\text{C}_6)\text{alkoxy}$;

X^{12} is hydrogen, $(\text{C}_1-\text{C}_6)\text{alkyl}$, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally

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substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

L¹ is C(X²)(X²), O, S(O)_m or N(X²);

5 r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5
10 halogens or 1 to 3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X⁶ for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally
15 substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted by, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl or 1 or 2 (C₁-C₄)alkyl; or

where there are two X⁶ groups on one atom and both X⁶ are (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the
20 two X⁶ groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X⁷ is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

25 X⁶ and X¹² cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²; and

when R² is hydrogen then R¹ is not -CH=CH-phenyl.

A group of intermediate compounds preferred among the foregoing group of formula (II), designated "Group AA", contains those compounds wherein w is 0 or 1;
30 n is 1; R¹ is hydrogen, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_t-A¹ or (C₁-C₁₀)alkyl where the (C₁-C₁₀)alkyl and (C₃-C₇)cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A¹ in the definition of R¹ is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, methoxy, CF₃, OCF₃

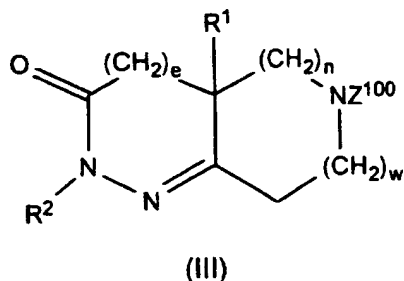
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and OCF_2H ; R^2 is hydrogen, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_0\text{-C}_3)\text{alkyl-(C}_3\text{-C}_7)\text{cycloalkyl}$, phenyl, or $(\text{C}_1\text{-C}_3)\text{alkyl-phenyl}$ where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3 , OH and methoxy.

- 5 A group of compounds preferred among the "AA Group" compounds, designated "BB Group", contains those compounds of "AA Group" wherein w is 1; e is 0; R^1 is $-\text{CH}_2\text{-pyridyl}$, $-\text{CH}_2\text{-thiazolyl}$, or $-\text{CH}_2\text{-phenyl}$ optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, $(\text{C}_1\text{-C}_4)\text{alkyl}$ or phenyl where the $(\text{C}_1\text{-C}_4)\text{alkyl}$ or phenyl groups in
10 the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy or methoxy.

- Compounds which are preferred among the "BB Group" compounds is the diastereomeric mixture of a compound wherein R^1 is $-\text{CH}_2\text{-phenyl}$ and R^2 is methyl or hydrogen; and the separated 3a-(R) and 3a-(S) isomers are preferred of the
15 diastereomeric mixture.

Another group of intermediate compounds which are useful in the synthesis of the compounds of formula (I) have the formula



- 20 the racemic-diastereomeric mixtures and optical isomers of said compounds wherein Z^{100} is methyl, BOC, CBZ, $\text{CF}_3\text{C(O)-}$, Fmoc, TROC, trityl, tosyl, $\text{CH}_3\text{C(O)-}$ or optionally substituted benzyl which optionally substituted with methoxy, dimethoxy or nitro; e is 0 or 1; n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;
- 25 R^1 is hydrogen, $-\text{CN}$, $-(\text{CH}_2)_q\text{N(X}^6\text{)C(O)X}^6$, $-(\text{CH}_2)_q\text{N(X}^6\text{)C(O)(CH}_2\text{)}_t\text{-A}^1$, $-(\text{CH}_2)_q\text{N(X}^6\text{)SO}_2(\text{CH}_2\text{)}_t\text{-A}^1$, $-(\text{CH}_2)_q\text{N(X}^6\text{)SO}_2\text{X}^6$, $-(\text{CH}_2)_q\text{N(X}^6\text{)C(O)N(X}^6\text{)(CH}_2\text{)}_t\text{-A}^1$, $-(\text{CH}_2)_q\text{N(X}^6\text{)C(O)N(X}^6\text{)(X}^6\text{)}$, $-(\text{CH}_2)_q\text{C(O)N(X}^6\text{)(X}^6\text{)}$, $-(\text{CH}_2)_q\text{C(O)N(X}^6\text{)(CH}_2\text{)}_t\text{-A}^1$, $-(\text{CH}_2)_q\text{C(O)OX}^6$, $-(\text{CH}_2)_q\text{C(O)O(CH}_2\text{)}_t\text{-A}^1$, $-(\text{CH}_2)_q\text{OX}^6$, $-(\text{CH}_2)_q\text{OC(O)X}^6$,

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- $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,
 $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$,
 $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$,
 $-(C_1-C_{10})alkyl$, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$,
5 $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;
where the alkyl and cycloalkyl groups in the definition of R^1 are optionally
substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $CONH_2$,
 $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$, 1H-tetrazol-5-yl or 1 to 3 fluoro;
 Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)$, $-C(O)NX^6$,
10 $-C(O)O$, $-OC(O)N(X^6)$ or $-OC(O)$;
q is 0, 1, 2, 3 or 4;
t is 0, 1, 2 or 3;
said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with
hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$,
15 $-CO_2(C_1-C_4)alkyl$, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 $(C_1-C_4)alkyl$;
 R^2 is hydrogen, $(C_1-C_8)alkyl$, $-(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkyl-A^1$ or A^1 ;
where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally
substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$,
 $-S(O)_m(C_1-C_6)alkyl$, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1 to 3 halogen;
20 A^1 for each occurrence is independently $(C_5-C_7)cycloalkenyl$, phenyl or a partially
saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally
having 1 to 4 heteroatoms independently selected from the group consisting of
oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially
saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally
25 having 1 to 4 heteroatoms independently selected from the group consisting of
nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully
unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms
independently selected from the group consisting of nitrogen, sulfur and oxygen;
 A^1 for each occurrence is independently optionally substituted, in one or
30 optionally both rings if A^1 is a bicyclic ring system, with up to three
substituents, each substituent independently selected from the group
consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$,
 $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, $(C_1-C_6)alkyl$, nitro, cyano, benzyl,

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-S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylen dioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶), -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1 to 3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X⁶ for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, (C₃-C₇)halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl,

-CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl or 1 or 2 (C₁-C₄)alkyl; or

where there are two X⁶ groups on one atom and both X⁶ are (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the

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two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

5 with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ;

when R^2 is hydrogen then R^1 is not $-CH=CH$ -phenyl;

when R^2 is H and R^1 is $-CH_2-CH=CH-Ph$, then Z^{100} is not BOC;

10 when R^2 is H and R^1 is then Z^{100} is not BOC;

when R^2 is H and R^1 is $-CH_2-C(CH_3)=CH_2$, then Z^{100} is not BOC; and

when R^2 is phenyl and R^1 is $-CH_3$, then Z^{100} is not $CH_3C(O)-$.

A group of compounds preferred among the foregoing group of compounds of formula (III), designated "CC Group", are those compounds wherein w is 0 or 1; n

15 is 1;

Z^{100} is BOC, methyl, benzyl or CBZ;

R^1 is hydrogen, $-(CH_2)_q-(C_3-C_7)$ cycloalkyl, $-(CH_2)_l-A^1$ or (C_1-C_{10}) alkyl where the (C_1-C_{10}) alkyl and (C_3-C_7) cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A^1 in the definition of R^1 is optionally substituted with 1 to 3 substituents

20 independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ;

R^2 is hydrogen, (C_1-C_8) alkyl, $-(C_0-C_3)$ alkyl- (C_3-C_7) cycloalkyl, phenyl, or $-(C_1-C_3)$ alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3 , OH and

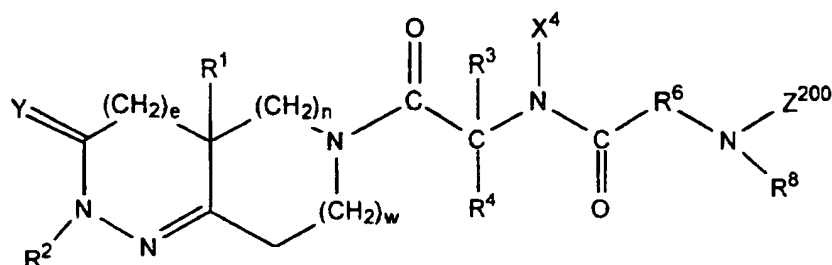
25 OMe.

A group of compounds preferred among the "CC Group" compounds, designated "DD Group", contains those compounds of "CC Group" wherein Z^{100} is BOC; w is 1; e is 0; R^1 is $-CH_2$ -pyridyl, $-CH_2$ -thiazolyl, or $-CH_2$ -phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, (C_1-C_4) alkyl or phenyl where the (C_1-C_4) alkyl or phenyl groups in the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy and methoxy.

30

Compounds which are preferred among the "DD Group" compounds is the diastereomeric mixture of a compound wherein R¹ is -CH₂-phenyl and R² is methyl or hydrogen; and the separated 3a-(R) and 3a-(S) isomers are preferred of the diastereomeric mixture.

5 Yet another group of compounds which are useful in the synthesis of the compounds of formula (I) contains those compounds of the formula



(IV)

the racemic-diastereomeric mixtures and optical isomers of said compounds wherein
10 Z^{200} is t-BOC, CBZ, $CF_3C(O)-$, Fmoc, Troc, trityl, tosyl or optionally substituted
benzyl which is optionally substituted with methoxy, dimethoxy or nitro;

e is 0 or 1:

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time:

15 Y is oxygen or sulfur;

R^1 is hydrogen, $-\text{CN}$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{X}^6$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{SO}_2(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{SO}_2\text{X}^6$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{OX}^6$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{O}(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{OX}^6$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{X}^6$, $-(\text{CH}_2)_q\text{OC}(\text{O})(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{OC}(\text{O})\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{X}^6$, $-(\text{CH}_2)_q\text{C}(\text{O})(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{C}(\text{O})\text{OX}^6$, $-(\text{CH}_2)_q\text{N}(\text{X}^6)\text{SO}_2\text{N}(\text{X}^6)(\text{X}^6)$, $-(\text{CH}_2)_q\text{S}(\text{O})_m\text{X}^6$, $-(\text{CH}_2)_q\text{S}(\text{O})_m(\text{CH}_2)_l\text{A}^1$, $-(\text{C}_1\text{-C}_{10})\text{alkyl}$, $-(\text{CH}_2)_l\text{A}^1$, $-(\text{CH}_2)_q\text{-(C}_3\text{-C}_7\text{)cycloalkyl}$, $-(\text{CH}_2)_q\text{-Y}^1\text{-(C}_1\text{-C}_6\text{)alkyl}$, $-(\text{CH}_2)_q\text{-Y}^1\text{-(CH}_2)_l\text{A}^1$ or $-(\text{CH}_2)_q\text{-Y}^1\text{-(CH}_2)_l\text{-(C}_3\text{-C}_7\text{)cycloalkyl}$;

25 where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;

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Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)$, $-C(O)NX^6$,
 $-C(O)O$, $-OC(O)N(X^6)$ or $-OC(O)$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

- 5 said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, (C_1-C_4) alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl, $-CO_2(C_1-C_4)$ alkyl, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 (C_1-C_4) alkyl;

R^2 is hydrogen, (C_1-C_8) alkyl, $-(C_0-C_3)$ alkyl- (C_3-C_8) cycloalkyl, $-(C_1-C_4)$ alkyl- A^1 or A^1 ;

- where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally
 10 substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1 to 3 halogen;

R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl,

$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl, $-(C_1-C_5)$ alkyl- X^1 - (C_0-C_5) alkyl- A^1 or

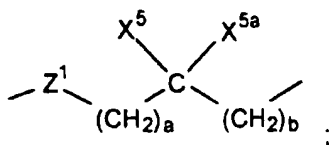
$-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl- (C_3-C_7) cycloalkyl;

- 15 where the alkyl groups in the definition of R^3 is optionally substituted with $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,
 $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

- R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and
 20 the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated
 25 or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;
 X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;

- 30 R^6 is a bond or is



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where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl in the definition of X^5 and X^{5a} is

5 optionally substituted with a substituent selected from the group consisting of A^1 , $-OX^2$, $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^2$, (C_3-C_7) cycloalkyl, $-N(X^2)(X^2)$ and $-C(O)N(X^2)(X^2)$;

or the carbon bearing X^5 and X^{5a} forms an alkylene bridge with the nitrogen atom bearing Z^{200} and R^8 where the alkylene bridge contains 1 to 5 carbon atoms provided that X^5 or X^{5a} but not both may be on the carbon atom and Z^{200} or R^8 but not both may be on the nitrogen atom;

10 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

15 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

20 Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

25 R^8 is hydrogen or optionally substituted (C_1-C_6) alkyl;

where the optionally substituted (C_1-C_6) alkyl in the definition of R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl,

30 $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or

A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of

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oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6) alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$ alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$, $-N(X^6)SO_2$ -phenyl, $-N(X^6)SO_2X^6$, $-CONX^{11}X^{12}$, $-SO_2NX^{11}X^{12}$, $-NX^6SO_2X^{12}$, $-NX^6CONX^{11}X^{12}$, $-NX^6SO_2NX^{11}X^{12}$, $-NX^6C(O)X^{12}$, imidazolyl, thiazolyl and tetrazolyl, provided that if A^1 is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X^{11} is hydrogen or optionally substituted (C_1-C_6) alkyl;

the optionally substituted (C_1-C_6) alkyl defined for X^{11} is optionally independently substituted with phenyl, phenoxy, (C_1-C_6) alkoxycarbonyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C_1-C_{10}) alkanoyloxy or 1 to 3 (C_1-C_6) alkoxy;

X^{12} is hydrogen, (C_1-C_6) alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X^{12} is not hydrogen, X^{12} is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH_3 , OCH_3 , OCF_3 and CF_3 ;

or X^{11} and X^{12} are taken together to form $-(CH_2)_r-L^1-(CH_2)_r$;

L^1 is $C(X^2)(X^2)$, O, $S(O)_m$ or $N(X^2)$;

r for each occurrence is independently 1, 2 or 3;

X^2 for each occurrence is independently hydrogen, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_3-C_7) cycloalkyl, where the optionally substituted (C_1-C_6) alkyl and optionally substituted (C_3-C_7) cycloalkyl in the definition of X^2 are

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optionally independently substituted with $-S(O)_m(C_1-C_6)alkyl$, $-C(O)OX^3$, 1 to 5 halogens or 1 to 3 $-OX^3$;

X^3 for each occurrence is independently hydrogen or $(C_1-C_6)alkyl$;

- X^6 for each occurrence is independently hydrogen, optionally substituted $(C_1-C_6)alkyl$, $(C_2-C_6)halogenated alkyl$, optionally substituted $(C_3-C_7)cycloalkyl$, $(C_3-C_7)halogenatedcycloalkyl$, where optionally substituted $(C_1-C_6)alkyl$ and optionally substituted $(C_3-C_7)cycloalkyl$ in the definition of X^6 is optionally independently substituted with hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$, 1H-tetrazol-5-yl or 1 or 2 $(C_1-C_4)alkyl$; or
- when there are two X^6 groups on one atom and both X^6 are $(C_1-C_6)alkyl$, the two $(C_1-C_6)alkyl$ groups may be optionally joined and, together with the atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or $(C_1-C_6)alkyl$ optionally substituted by hydroxyl; and

- m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

- when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is 2 or 3.

Compounds which are preferred of the foregoing compounds of formula (IV) is the compound wherein e is 0; Y is O; R^1 is $-CH_2$ -phenyl; R^2 is methyl or hydrogen; n is 1; w is 1; R^3 is $-CH_2-O-CH_2$ -phenyl; R^4 is hydrogen; X^4 is hydrogen; R^6 is $-C(CH_3)_2-$; Z^{200} is BOC and R^8 is hydrogen.

- This invention also provides:

a method for increasing levels of endogenous growth hormone in a human or other animal which comprises administering to such human or other animal an effective amount of a compound of Formula I;

- a pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an inert carrier and an effective amount of a compound of Formula I;

a pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which

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comprises an inert carrier, an effective amount of a compound of Formula I and another growth hormone secretagogue such as, GHRP-6, Hexarelin, GHRP-1, IGF-1, IGF-2, B-HT920 or growth hormone releasing factor (GRF) or an analog thereof;

5 a method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in treating or preventing osteoporosis;

a method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of a
10 bisphosphonate compound such as alendronate, and especially preferred is the bisphosphonate compound ibandronate, and a compound of Formula I;

a method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of estrogen or Premarin® and a compound of Formula I and optionally progesterone;

15 a method to increase IGF-1 levels in IGF-1 deficient humans or other animals which comprises administering to a human or other animal with IGF-1 deficiency a compound of Formula I;

a method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of an estrogen agonist or
20 antagonist such as tamoxifen, droloxifene, raloxifene and idoxifene and a compound of Formula I;

a particularly preferred method for the treatment of osteoporosis comprises administering to a human or other animal with osteoporosis a combination of an estrogen agonist or antagonist such as *Cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

25 (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

30 *cis*-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

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cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-isoquinoline and a compound of Formula I;

5 a method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of calcitonin and a compound of Formula I;

 a method for increasing muscle mass, which method comprises administering to a human or other animal in need of such treatment an amount of a compound of
10 Formula I which is effective in promoting release of endogenous growth hormone; and

 a method for promoting growth in growth hormone deficient children which comprises administering to a growth hormone deficient child a compound of Formula I which is effective in promoting release of endogenous growth hormone.

15 This invention further provides a method for treating or preventing diseases or conditions which may be treated or prevented by growth hormone which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone.

20 In another aspect, this invention provides methods for treating or preventing congestive heart failure, frailty associated with aging, and obesity which comprise administering to a human or other animal in need of such treatment or prevention an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone; of the instant method it is preferred that the disease or
25 condition to be treated or prevented is congestive heart failure or frailty associated with aging.

 In another aspect, this invention provides methods for accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness such as AIDS and cancer,
30 accelerating wound healing, and accelerating the recovery of burn patients or patients having undergone major surgery, which comprise administering to a human or other animal in need of such treatment an amount of a compound of Formula I which is effective in promoting release of endogenous growth hormone; of the instant

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method a preferred method of use is to accelerate bone fracture repair or for accelerating the recovery of patients having undergone major surgery.

In yet another aspect, this invention provides methods for improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis and renal
5 homeostasis, which comprise administering to a human or other animal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

The instant compounds promote the release of growth hormone which are stable under various physiological conditions and may be administered parenterally,
10 nasally or by the oral route.

Detailed Description of the Invention

One of ordinary skill will recognize that certain substituents listed in this invention may have reduced chemical stability when combined with one another or with heteroatoms in the compounds. Such compounds with reduced chemical
15 stability are not preferred.

In general the compounds of Formula I can be made by processes which include processes known in the chemical arts for the production of compounds. Certain processes for the manufacture of Formula I compounds are provided as further features of the invention and are illustrated by the following reaction
20 schemes.

In the above structural formulae and throughout the instant application, the following terms have the indicated meanings unless expressly stated otherwise:

The alkyl groups are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain
25 double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, ethynyl, propenyl, butadienyl, hexenyl and the like.

When the definition C₀-alkyl occurs in the definition, it means a single covalent bond.

30 The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy,

isopentoxy, hexoxy, isohexoxy, allyloxy, 2-propynyloxy, isobutenyloxy, hexenyloxy and the like.

The term "halogen" or "halo" is intended to include the halogen atoms fluorine, chlorine, bromine and iodine.

- 5 The term "halogenated alkyl" is intended to include an alkyl group as defined hereinabove substituted by one or more halogen atoms as defined hereinabove.

The term "halogenated cycloalkyl" is intended to include a cycloalkyl group substituted by one or more halogen atoms as defined hereinabove.

- 10 The term "aryl" is intended to include phenyl and naphthyl and aromatic 5- and 6-membered rings with 1 to 4 heteroatoms or fused 5- or 6-membered bicyclic rings with 1 to 4 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic aromatic rings are pyridine, thiophene (also known as thienyl), furan, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, pyrimidine, and thiadiazole.

- 15 The chemist of ordinary skill will recognize that certain combinations of heteroatom-containing substituents listed in this invention define compounds which will be less stable under physiological conditions (e.g., those containing acetal or aминаl linkages). Accordingly, such compounds are less preferred.

- 20 The expression "prodrug" refers to compounds that are drug precursors, which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). Exemplary prodrugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of this invention include but are not limited to carboxylic acid substituents
25 (e.g., R^1 is $-(CH_2)_qC(O)_2X^6$ where X^6 is hydrogen, or R^2 or A^1 contains carboxylic acid) wherein the free hydrogen is replaced by (C_1-C_4) alkyl, (C_2-C_{12}) alkanoyloxymethyl, $(C_4-C_9)1-(alkanoyloxy)ethyl$, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-
30 methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl

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(such as β -dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)-alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

Other exemplary prodrugs release an alcohol of Formula I wherein the free hydrogen of the hydroxyl substituent (e.g., R¹ contains hydroxyl) is replaced by (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxy-carbonylamino-methyl, succinoyl, (C₁-C₆)alkanoyl, α -amino(C₁-C₄)alkanoyl, arylacetyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl wherein said α -aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate).

Prodrugs of this invention where a carboxyl group in a carboxylic acid of Formula (I) is replaced by an ester may be prepared by combining the carboxylic acid with the appropriate alkyl halide in the presence of a base such as potassium carbonate in an inert solvent such as DMF at a temperature of about 0°C to 100°C for about 1 to about 24 hours. Alternatively, the acid is combined with the appropriate alcohol as solvent in the presence of a catalytic amount of acid such as concentrated sulfuric acid at a temperature of about 20°C to 120°C, preferably at reflux, for about 1 hour to about 24 hours. Another method is the reaction of the acid in an inert solvent such as THF, with concomitant removal of the water being produced by physical (e.g., Dean Stark trap) or chemical (e.g., molecular sieves) means.

Prodrugs of this invention where an alcohol function has been derivatized as an ether may be prepared by combining the alcohol with the appropriate alkyl bromide or iodide in the presence of a base such as potassium carbonate in an inert solvent such as DMF at a temperature of about 0°C to 100°C for about 1 to about 24 hours. Alkanoylaminomethyl ethers may be obtained by reaction of the alcohol with a bis-(alkanoylamino)methane in the presence of a catalytic amount of acid in an inert solvent such as THF, according to a method described in US 4,997,984. Alternatively, these compounds may be prepared by the methods described by Hoffman et al. in J. Org. Chem. 1994, 59, p. 3530.

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Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Throughout the specification and appendent claims the following
5 abbreviations are used with the following meanings:

	BOC	t-butyloxycarbonyl
	BOP	Benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate
	CBZ	Benzyloxycarbonyl
10	CDI	N,N'-Carbonyldiimidazole
	CH ₂ Cl ₂	Methylene chloride
	CHCl ₃	Chloroform
	DCC	Dicyclohexylcarbodiimide
	DMF	Dimethylformamide
15	EDC	1-(3-dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride
	EtOAc	Ethyl acetate
	FMOC	9-Fluorenylmethoxycarbonyl
	h	hours
20	Hex	Hexane
	HOAT	1-Hydroxy-7-azabenzotriazole
	HOBT	Hydroxybenzotriazole hydrate
	HPLC	High pressure liquid chromatography
	MHz	Megahertz
25	MS	Mass Spectrum
	NMR	Nuclear Magnetic Resonance
	PTH	Parathyroid hormone
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
30	TLC	Thin layer chromatography

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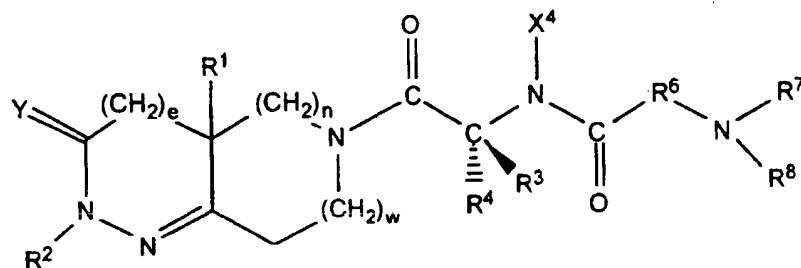
TRH

Thyrotropin releasing hormone

TROC

2,2,2-Trichloroethoxycarbonyl

The compounds of the instant invention all have at least one asymmetric center as noted by the asterisk in the structural Formula I, above. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diastereomeric mixtures thereof, be included within the scope of the instant invention. In the case of the asymmetric center represented by the asterisk, it has been found that the absolute stereochemistry of the more active and thus more preferred isomer is shown in Formula IA. This preferred absolute configuration also applies to Formula I.



(IA)

With the R⁴ substituent as hydrogen, the spatial configuration of the asymmetric center corresponds to that in a D-amino acid. In most cases this is also designated an R-configuration although this will vary according to the values of R³ and R⁴ used in making R- or S-stereochemical assignments.

The instant compounds are generally isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfuric, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, D-tartaric, L-tartaric, malonic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their inorganic salt in which the counter-ion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The pharmaceutically acceptable salts are formed by taking about 1 equivalent of a compound of formula (I) and contacting it with about 1 equivalent of

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the appropriate corresponding acid of the salt which is desired. Work-up and isolation of the resulting salt is well-known to those of ordinary skill in the art.

Th growth hormone releasing compounds of Formula I are useful *in vitro* as unique tools for understanding how growth hormone secretion is regulated at the pituitary level. This includes use in the evaluation of many factors thought or known to influence growth hormone secretion such as age, sex, nutritional factors, glucose, amino acids, fatty acids, as well as fasting and non-fasting states. In addition, the compounds of this invention can be used in the evaluation of how other hormones modify growth hormone releasing activity. For example, it has already been established that somatostatin inhibits growth hormone release.

The compounds of Formula I can be administered to animals, including humans, to release growth hormone *in vivo*. The compounds are useful for treatment of symptoms related to GH deficiency; stimulate growth or enhance feed efficiency of animals raised for meat production to improve carcass quality; to increase milk production in dairy cattle; improvement of bone or wound healing and improvement in vital organ function. The compounds of the present invention by inducing endogenous GH secretion will alter body composition and modify other GH-dependent metabolic, immunologic or developmental processes. For example, the compounds of the present invention can be given to chickens, turkeys, livestock animals (such as sheep, pigs, horses, cattle, etc.), companion animals (e.g., dogs) or may have utility in aquaculture to accelerate growth and improve the protein/fat ratio. In addition, these compounds can be administered to humans *in vivo* as a diagnostic tool to directly determine whether the pituitary is capable of releasing growth hormone. For example, the compounds of Formula I can be administered *in vivo* to children. Serum samples taken before and after such administration can be assayed for growth hormone. Comparison of the amounts of growth hormone in each of these samples would be a means for directly determining the ability of the patient's pituitary to release growth hormone.

Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of Formula I in association with a pharmaceutically acceptable carrier. Optionally, the pharmaceutical compositions can further comprise an anabolic agent in addition to at least one of the compounds of Formula I or another compound which exhibits a

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different activity, e.g., an antibiotic growth permittant or an agent to treat osteoporosis or with other pharmaceutically active materials wherein the combination enhances efficacy and minimizes side effects.

Growth promoting and anabolic agents include, but are not limited to, TRH,
5 PTH, diethylstilbesterol, estrogens, β -agonists, theophylline, anabolic steroids, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, the disclosure of which is hereby incorporated by reference, e.g., zeranol; compounds disclosed in U.S. Patent No. 4,036,979, the disclosure of which is hereby incorporated by reference, e.g., sulbenox; and peptides disclosed in U.S. Patent No.
10 4,411,890, the disclosure of which is hereby incorporated by reference.

The growth hormone secretagogues of this invention in combination with other growth hormone secretagogues such as the growth hormone releasing peptides GHRP-6 and GHRP-1 as described in U.S. Patent No. 4,411,890, the disclosure of which is hereby incorporated by reference, and publications WO
15 89/07110, WO 89/07111 and B-HT920 as well as hexarelin and the newly discovered GHRP-2 as described in WO 93/04081 or growth hormone releasing hormone (GHRH, also designated GRF) and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2 or μ -adrenergic agonists such as clonidine or serotonin 5HT_{1D} agonists such as sumatriptan or agents which inhibit
20 somatostatin or its release such as physostigmine and pyridostigmine, are useful for increasing the endogenous levels of GH in mammals. The combination of a GH secretagogue of this invention with GRF results in synergistic increases of endogenous growth hormone.

As is well known to those skilled in the art, the known and potential uses of
25 growth hormone are varied and multitudinous [See "Human Growth Hormone", Strobel and Thomas, *Pharmacological Reviews*, **46**, pg. 1-34 (1994); T. Rosen et al., *Horm Res*, 1995; **43**: pp. 93-99; M. Degerblad et al., *European Journal of Endocrinology*, 1995, **133**: pp.180-188; J. O. Jorgensen, *European Journal of Endocrinology*, 1994, **130**: pp. 224-228; K. C. Copeland et al., *Journal of Clinical Endocrinology and Metabolism*, Vol. 78 No. 5, pp. 1040-1047; J. A. Aloï et al.,
30 *Journal of Clinical Endocrinology and Metabolism*, Vol. 79 No. 4, pp. 943-949; F. Cordido et al., *Metab. Clin. Exp.*, (1995), **44**(6), pp. 745-748; K. M. Fairhall et al., *J. Endocrinol.*, (1995), **145**(3), pp. 417-426; R.M. Frieboes et al.,

Neuroendocrinology, (1995), 61(5), pp. 584-589; and M. Llovera et al., *Int. J. Canc r*, (1995), 61(1), pp. 138-141]. Thus, the administration of the compounds of this invention for purposes of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows: stimulating growth hormone release in elderly humans; treating growth hormone deficient adults; preventing catabolic side effects of glucocorticoids, treating osteoporosis, stimulating the immune system, acceleration of wound healing, accelerating bone fracture repair, treating growth retardation, treating congestive heart failure as disclosed in PCT publications WO 95/28173 and WO 95/28174 (an example of a method for assaying growth hormone secretagogues for efficacy in treating congestive heart failure is disclosed in R. Yang et al., *Circulation*, Vol. 92, No. 2, p.262, 1995), treating acute or chronic renal failure or insufficiency, treatment of physiological short stature, including growth hormone deficient children, treating short stature associated with chronic illness, treating obesity, treating growth retardation associated with Prader-Willi syndrome and Turner's syndrome; accelerating the recovery and reducing hospitalization of burn patients or following major surgery such as gastrointestinal surgery; treating intrauterine growth retardation, skeletal dysplasia, hypercortisonism and Cushings syndrome; replacing growth hormone in stressed patients; treating osteochondrodysplasias, Noonans syndrome, sleep disorders, Alzheimer's disease, delayed wound healing, and psychosocial deprivation; treating of pulmonary dysfunction and ventilator dependency; attenuating protein catabolic response after a major operation; treating malabsorption syndromes, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; accelerating weight gain and protein accretion in patients on TPN (total parenteral nutrition); treating hyperinsulinemia including nesidioblastosis; adjuvant treatment for ovulation induction and to prevent and treat gastric and duodenal ulcers; stimulating thymic development and preventing age-related decline of thymic function; adjunctive therapy for patients on chronic hemodialysis; treating immunosuppressed patients and enhancing antibody response following vaccination; improving muscle strength, increasing muscle mass, mobility, maintenance of skin thickness, metabolic homeostasis, renal hemeostasis in the frail elderly; stimulating osteoblasts, bone remodelling, and cartilage growth; treating neurological diseases such as peripheral

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and drug induced neuropathy, Guillian-Barre Syndrome, amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular accidents and demyelinating diseases; stimulating the immune system in companion animals and treating disorders of aging in companion animals; growth promotant in livestock; and stimulating wool growth in
5 sheep.

It will be known to those skilled in the art that there are numerous compounds now being used in an effort to treat the diseases or therapeutic indications enumerated above. Combinations of these therapeutic agents, some of which have also been mentioned above, with the growth promotant, exhibit anabolic and
10 desirable properties of these various therapeutic agents. In these combinations, the therapeutic agents and the growth hormone secretagogues of this invention may be independently and sequentially administered or co-administered in dose ranges from one one-hundredth to one times the dose levels which are effective when these compounds and secretagogues are used singly. Combined therapy to inhibit bone
15 resorption, prevent osteoporosis, reduce skeletal fracture, enhance the healing of bone fractures, stimulate bone formation and increase bone mineral density can be effectuated by combinations of bisphosphonates and the growth hormone secretagogues of this invention, see PCT publication WO 95/11029 for a discussion of combination therapy using bisphosphonates and GH secretagogues. The use of
20 bisphosphonates for these utilities has been reviewed, for example, by Hamdy, N.A.T., Role of Bisphosphonates in Metabolic Bone Diseases, **Trends in Endocrinol. Metab.**, 1993, 4, pages 19-25. Bisphosphonates with these utilities include but are not limited to alendronate, tiludronate, dimethyl-APD, risedronate, etidronate, YM-175, clodronate, pamidronate, and BM-210995 (ibandronate).
25 According to their potency, oral daily dosage levels of the bisphosphonate of between 0.1 mg and 5 g and daily dosage levels of the growth hormone secretagogues of this invention of between 0.01 mg/kg to 20 mg/kg of body weight are administered to patients to obtain effective treatment of osteoporosis.

The compounds of this invention may be combined with a mammalian estrogen
30 agonist/antagonist. Any estrogen agonist/antagonist may be used as the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds

capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art according to standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods (see Eriksen E.F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S.J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H.W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below, however, other estrogen agonists/antagonists will be known to those skilled in the art. A preferred estrogen agonist/antagonist is droloxifene: (phenol, 3-[1-[4[2-(dimethylamino)ethoxy]-phenyl]-2-phenyl-1-butenyl]-, (E)-) and associated compounds which are disclosed in U.S. patent 5,047,431 (the disclosure of which is hereby incorporated by reference).

Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)) and associated compounds which are disclosed in U.S. patent 4,536,516 (the disclosure of which is hereby incorporated by reference). Another related compound is 4-hydroxy tamoxifen which is disclosed in U.S. patent 4,623,660 (the disclosure of which is hereby incorporated by reference).

Another preferred estrogen agonist/antagonist is raloxifene: (methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyloxy)phenyl]-, hydrochloride) and associated compounds which are disclosed in U.S. patent 4,418,068 (the disclosure of which is hereby incorporated by reference).

Another preferred estrogen agonist/antagonist is idoxifene: Pyrrolidine, 1-[4-[[1-(4-iodophenyl)-2-phenyl-1-Butenyl]phenoxy]ethyl] and associated compounds which are disclosed in U.S. patent 4,839,155 (the disclosure of which is hereby incorporated by reference).

Other preferred estrogen agonist/antagonists include compounds as described in commonly assigned U.S. patent no. 5,552,412 the disclosure of which is hereby

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incorporated by reference. Especially preferred compounds which are described therein are:

cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol;

5 (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol;

cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol;

10 *cis*-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4''-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; and

15 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline.

Other estrogen agonist/antagonists are described in U.S. Patent 4,133,814 (the disclosure of which is hereby incorporated by reference). U.S. Patent 4,133,814 discloses derivatives of 2-phenyl-3-aryl-benzothiophene and 2-phenyl-3-
20 arylbenzothiophene-1-oxide.

The following paragraphs provide preferred dosage ranges for various anti-resorptive agents.

The amount of the anti-resorptive agent to be used is determined by its activity as a bone loss inhibiting agent. This activity is determined by means of an individual
25 compound's pharmacokinetics and its minimal maximal effective dose in inhibition of bone loss using a protocol such as those referenced above.

In general an effective dosage for the activities of this invention, for example the treatment of osteoporosis, for the estrogen agonists/antagonists (when used in combination with a compound of Formula I of this invention) is in the range of 0.01 to
30 200 mg/kg/day, preferably 0.5 to 100 mg/kg/day.

In particular, an effective dosage for droloxifene is in the range of 0.1 to 40 mg/kg/day, preferably 0.1 to 5 mg/kg/day.

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In particular, an effective dosage for raloxifene is in the range of 0.1 to 100 mg/kg/day, preferably 0.1 to 10 mg/kg/day.

In particular, an effective dosage for tamoxifen is in the range of 0.1 to 100 mg/kg/day, preferably 0.1 to 5 mg/kg/day.

5 In particular, an effective dosage for

cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

(-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

10 *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

15 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or

1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-

20 tetrahydroisoquinoline is in the range of 0.0001 to 100 mg/kg/day, preferably 0.001 to 10 mg/kg/day.

In particular, an effective dosage for 4-hydroxy tamoxifen is in the range of 0.0001 to 100 mg/kg/day, preferably 0.001 to 10 mg/kg/day.

Compounds that have the ability to stimulate GH secretion from cultured rat pituitary cells are identified using the following protocol. This test is also useful for
25 comparison to standards to determine dosage levels. Cells are isolated from pituitaries of 6-week old male Wistar rats. Following decapitation, the anterior pituitary lobes are removed into cold, sterile Hank's balanced salt solution without calcium or magnesium (HBSS). Tissues are finely minced, then subjected to two cycles of mechanically assisted enzymatic dispersion using 10 U/mL bacterial
30 protease (EC 3.4.24.4, Sigma P-6141) in HBSS. The tissue-enzyme mixture is stirred in a spinner flask at 30 rpm in a 5% CO₂ atmosphere at about 37°C for about 30 min, with manual trituration after about 15 min and about 30 min using a 10-mL

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pipet. This mixture is centrifuged at 200 x g for about 5 min. Horse serum is added to the supernatant to neutralize excess protease. The pellet is resuspended in fresh protease, stirred for about 30 min more under the previous conditions, and manually triturated, ultimately through a 23-gauge needle. Again, horse serum is added, then

5 the cells from both digests are combined, pelleted (200 x g for about 15 min), washed, resuspended in culture medium and counted. Cells are plated at $6.0\text{--}6.5 \times 10^4$ cells per cm^2 in 48-well Costar dishes and cultured for 3-4 days in Dulbecco's Modified Eagle Medium (D-MEM) supplemented with 4.5 g/L glucose, 10% horse serum, 2.5% fetal bovine serum, 1% non-essential amino acids, 100

10 U/mL nystatin and 50 mg/mL gentamycin sulfate before assaying for GH secretion.

Just prior to assay, culture wells are rinsed twice, then equilibrated for about 30 minutes in release medium (D-MEM buffered with 25 mM Hepes, pH 7.4 and containing 0.5% bovine serum albumin at 37°C). Test compounds are dissolved in DMSO, then diluted into pre-warmed release medium. Assays are run in

15 quadruplicate. The assay is initiated by adding 0.5 mL of release medium (with vehicle or test compound) to each culture well. Incubation is carried out at about 37°C for about 15 minutes, then terminated by removal of the culture medium, which is centrifuged at 2000 x g for about 15 minutes to remove cellular material. Rat growth hormone concentrations in the supernatants are determined by a standard

20 radioimmunoassay protocol using a rat growth hormone reference preparation (NIDDK-rGH-RP-2) and rat growth hormone antiserum raised in monkey (NIDDK-anti-rGH-S-5) obtained from Dr. A. Parlow (Harbor-UCLA Medical Center, Torrance, CA). Additional rat growth hormone (1.5U/mg, #G2414, Scripps Labs, San Diego, CA) is iodinated to a specific activity of approximately 30 $\mu\text{Ci}/\mu\text{g}$ by the chloramine T

25 method for use as tracer. Immune complexes are obtained by adding goat antiserum to monkey IgG (Organon Teknika, Durham, NC) plus polyethylene glycol, MW 10,000-20,000 to a final concentration of 4.3%; recovery is accomplished by centrifugation. This assay has a working range of 0.08-2.5 μg rat growth hormone per tube above basal levels. Active compounds typically stimulate growth hormone

30 release by greater than 1.4 fold. Reference: Cheng, K., Chan, W.-S., Barreto, Jr., A., Convey, E.M., Smith, R.G. 1989.

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Assay for Exogenously-Stimulated Growth Hormone Release in the Rat after Intravenous Administration of Test Compounds

Twenty-one day old female Sprague-Dawley rats (Charles River Laboratory, Wilmington, MA) are allowed to acclimate to local vivarium conditions (24 °C, 12 hr light, 12 hr dark cycle) for approximately 1 week before compound testing. All rats are allowed access to water and a pelleted commercial diet (Agway Country Food, Syracuse NY) *ad libitum*. The experiments are conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

On the day of the experiment, test compounds are dissolved in vehicle containing 1% ethanol, 1mM acetic acid and 0.1% bovine serum albumin in saline. Each compound is tested with n=3. Rats are weighed and anesthetized via intraperitoneal injection of sodium pentobarbital (Nembutol, 50 mg/kg body weight). Fourteen minutes after anesthetic administration, a blood sample is taken by nicking the tip of the tail and allowing the blood to drip into a microcentrifuge tube (baseline blood sample, approximately 100 µl). Fifteen minutes after anesthetic administration, test compound is delivered by intravenous injection into the tail vein, with a total injection volume of 1 ml/kg body weight. Additional blood samples are taken from the tail at 5, 10 and 15 minutes after compound administration. Blood samples are kept on ice until serum separation by centrifugation (1430xg for 10 minutes at 10°C). Serum is stored at -80°C until serum growth hormone determination by radio-immunoassay as described above and below.

Assessment of Exogenously-Stimulated Growth Hormone Release in the Dog after Oral Administration

On the day of experimentation, the test compound is weighed out for the appropriate dose and dissolved in water. Doses are delivered at a volume of 0.5 ml/kg by gavage to 4 dogs for each dosing regimen. Blood samples (2 ml) are collected from the jugular vein by direct vena puncture pre-dose and at 0.08, 0.17, 0.25, 0.5, 0.75, 1, 2, 4, 6, and 8 hours post dose using 2 ml vacutainers containing lithium heparin. The prepared plasma is stored at -20 °C until analysis.

Measurement of Canine Growth Hormone

Canine growth hormone concentrations are determined by a standard radioimmunoassay protocol using canine growth hormone (antigen for iodination and

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reference preparation AFP-1983B) and canine growth hormone antiserum raised in monkey (AFP-21452578) obtained from Dr. A. Parlow (Harbor-UCLA Medical Center, Torrance, CA). Tracer is produced by chloramine T-iodination of canine growth hormone to a specific activity of 20-40 $\mu\text{Ci}/\mu\text{g}$. Immune complexes are
5 obtained by adding goat antiserum to monkey IgG (Organon Teknika, Durham, NC) plus polyethylene glycol, MW 10,000-20,000 to a final concentration of 4.3%; recovery is accomplished by centrifugation. This assay has a working range of 0.08-2.5 μg canine GH/tube.

The compounds of this invention can be administered by oral, parenteral
10 (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual, or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills,
15 powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms
20 may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents,
25 compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol,
30 vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing

agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

- 5 Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as cocoa butter or a suppository wax.

 Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

- 10 The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 0.0001 to 100 mg/kg of body weight
15 daily are administered to humans and other animals, e.g., mammals, to obtain effective release of growth hormone.

 A preferred dosage range is 0.01 to 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

- The preparation of the compounds of Formula I of the present invention can
20 be carried out in sequential or convergent synthetic routes. Syntheses detailing the preparation of the compounds of Formula I in a sequential manner are presented in the reaction schemes shown hereinbelow.

- Many protected amino acid derivatives are commercially available, where the protecting groups Prt , Z^{100} and Z^{200} are, for example, BOC, CBZ, benzyl, ethoxycarbonyl groups, $CF_3C(O)-$, FMOC, TROC, trityl or tosyl. Other protected
25 amino acid derivatives can be prepared by literature methods. Some 3-oxo-2-carboxyl pyrrolidines, and 4-oxo-3-carboxyl piperidines are commercially available, and many other related pyrrolidines and 4-substituted piperidines are known in the literature.

- 30 Many of the schemes illustrated below describe compounds which contain protecting groups Prt , Z^{100} or Z^{200} . Benzyloxycarbonyl groups can be removed by a number of methods including, catalytic hydrogenation with hydrogen in the presence of a palladium or platinum catalyst in a protic solvent such as methanol. Preferred

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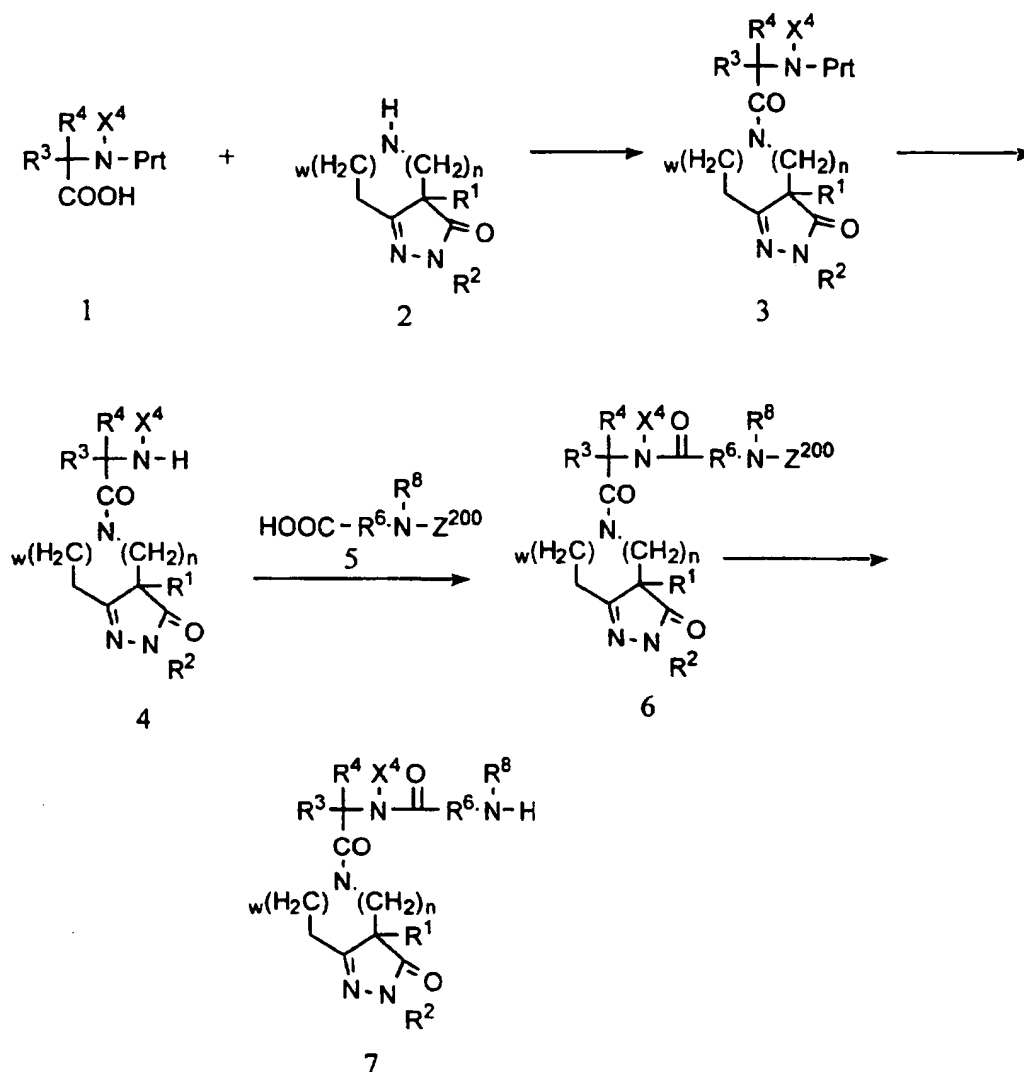
catalysts are palladium hydroxide on carbon or palladium on carbon. Hydrogen pressures from 1-1000 psi may be employed; pressures from 10 to 70 psi are preferred. Alternatively, the benzyloxycarbonyl group can be removed by transfer hydrogenation.

- 5 Removal of BOC protecting groups can be carried out using a strong acid such as trifluoroacetic acid or hydrochloric acid with or without the presence of a cosolvent such as dichloromethane, ethyl acetate, ether or methanol at a temperature of about -30 to 70°C, preferably about -5 to about 35°C.

- 10 Benzyl esters of amines can be removed by a number of methods including, catalytic hydrogenation with hydrogen in the presence of a palladium catalyst in a protic solvent such as methanol. Hydrogen pressures from 1-1000 psi may be employed; pressures from 10 to 70 psi are preferred. The addition and removal of these and other protecting groups are discussed by T. Greene in Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1981.

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SCHEME 1



SCHEME 1: The protected amino acid derivatives 1 are in many cases commercially available, where the protecting group Prt is, for example, BOC, FMOC or CBZ groups. Other amino acids can be prepared by literature methods.

As illustrated in Scheme 1, coupling of amines of formula 2 with protected amino acids of formula 1, where Prt is a suitable protecting group, is conveniently carried out in an inert solvent such as dichloromethane or DMF by a coupling reagent such as EDC or DCC in the presence of HOBT or HOAT. In the case where the amine is present as the hydrochloride salt, it is preferable to add one or two equivalents of a suitable base such as triethylamine to the reaction mixture.

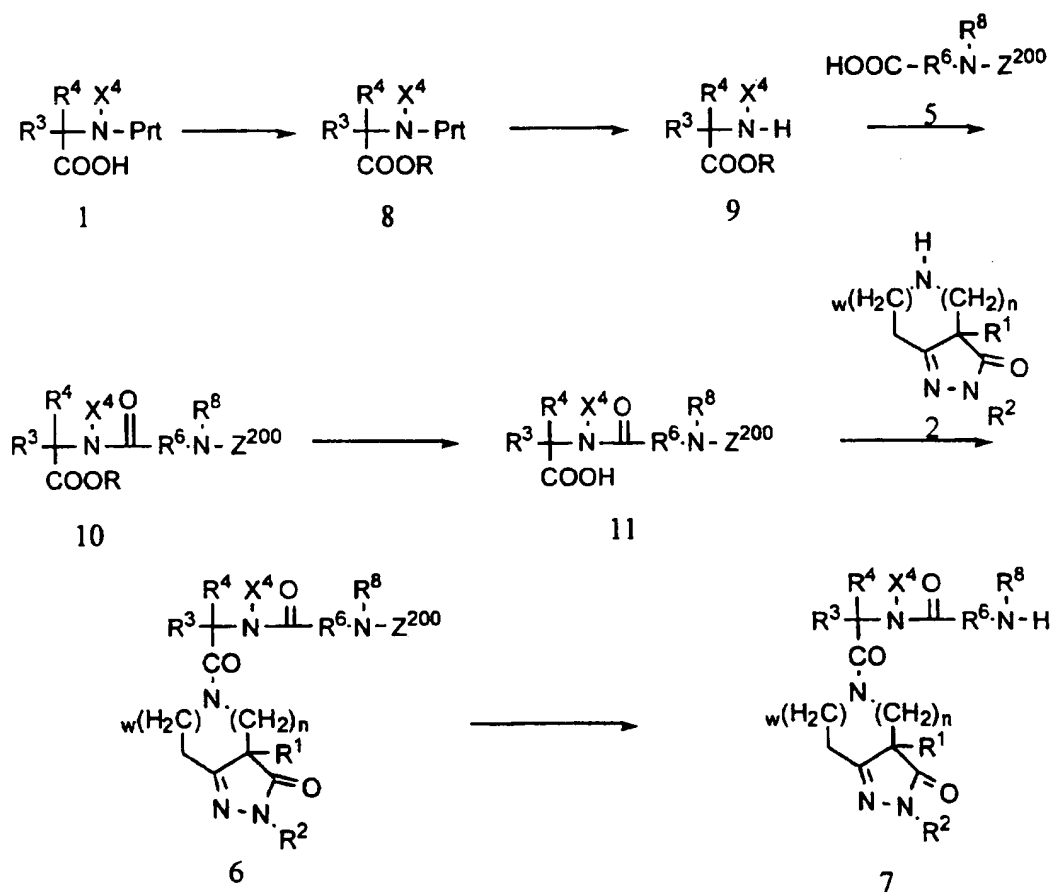
-49-

Alternatively, the coupling can be effected with a coupling reagent such as BOP in an inert solvent such as methanol. Such coupling reactions are generally conducted at temperatures of about -30° to about 80°C, preferably -10° to about 25°C. For a discussion of other conditions used for coupling peptides see Houben-Weyl, Vol.

- 5 XV, part II, E. Wunsch, Ed., George Theime Verlag, 1974, Stuttgart. Separation of unwanted side products and purification of intermediates is achieved by chromatography on silica gel, employing flash chromatography (W. C. Still, M. Kahn and A. Mitra, J. Org. Chem. 43 2923 1978), by crystallization or by trituration.

Transformation of the compound of formula 3 into intermediates of formula 4
10 can be carried out by removal of the protecting group Prt as described above. Coupling of intermediates of formula 4 to amino acids of formula 5 can be effected as described above to give intermediates of formula 6. Deprotection of the amine 6 affords compounds of formula 7.

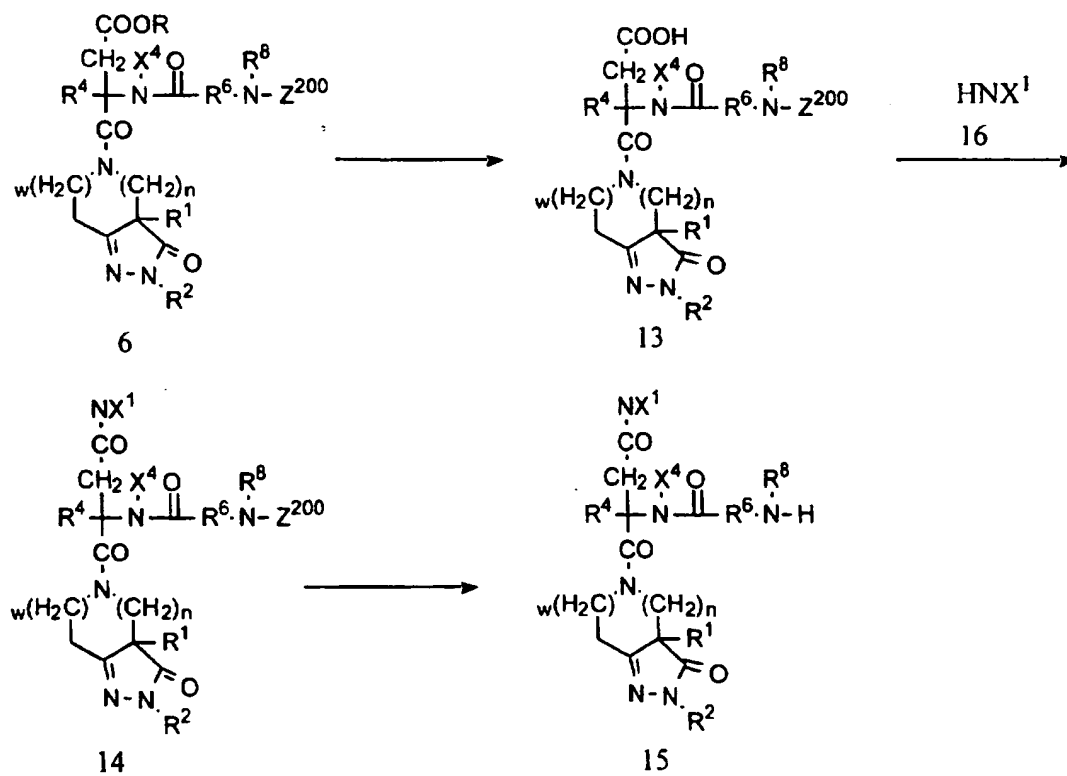
SCHEME 2



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SCHEME 2: Alternatively, compounds of formula 7 can be prepared by a convergent route as shown in Scheme 2. Intermediate esters of formula 8 can be prepared by treating amino acids 1, where Prt is a suitable protecting group, with a base such as potassium carbonate followed by an alkyl halide such as iodomethane in a suitable solvent such as DMF. Deprotection of the amine transforms 8 into 9. Alternatively, many amino acids of formula 9 are commercially available. Intermediate 10 is generated by coupling 9 to amino acid 5. The ester of intermediate 10 can be converted to intermediate acid 11 by a number of methods known in the art; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent such as aqueous methanol or aqueous THF at a temperature of about -20° to 120°C, preferably about 0° to 50°C. In addition, removal of a benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent such as methanol. Acid 11 can then be coupled to amine 2 to give intermediates of formula 6. Transformation of 6 to 7 can be achieved by removal of the protecting group Z²⁰⁰.

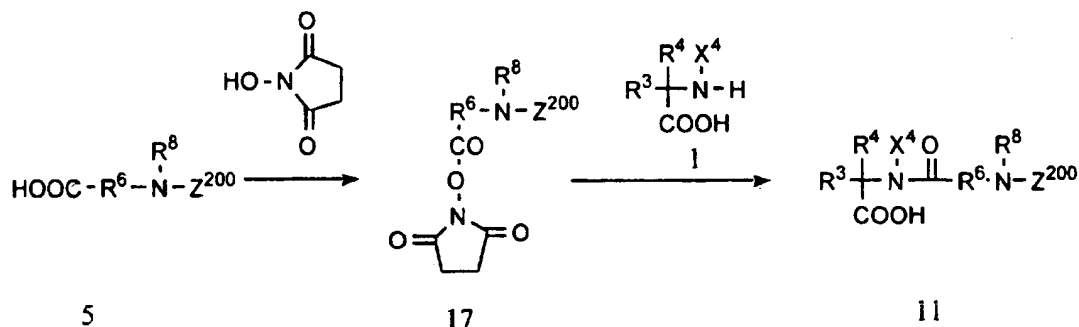
SCHEME 3



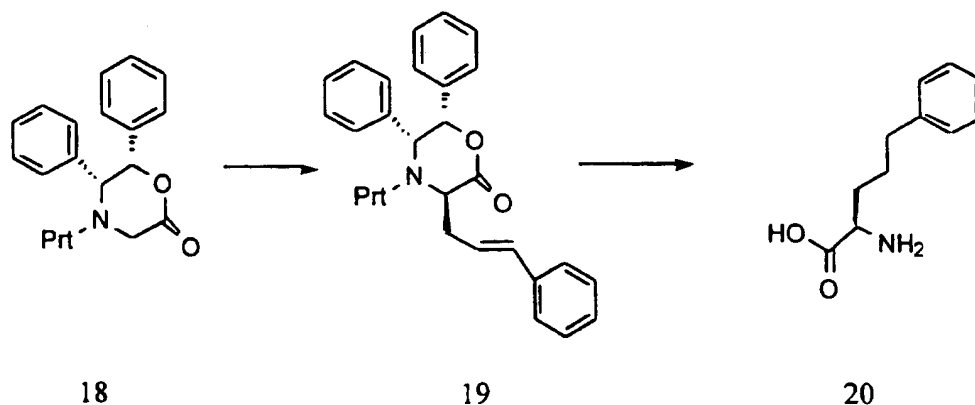
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SCHEME 3: The esters of formula 6 can be converted to intermediate acids of formula 13 by a number of methods known in the art; for example, methyl and ethyl esters can be hydrolyzed with lithium hydroxide in a protic solvent such as aqueous methanol or aqueous THF at a temperature of about -20° to 120°C, preferably about 0° to 50°C. In addition, removal of a benzyl group can be accomplished by a number of reductive methods including hydrogenation in the presence of platinum or palladium catalyst in a protic solvent such as methanol. Coupling the acid 13 to amine 16 generates the intermediates of formula 14. Transformation of 14 to 15 can be achieved by removal of the protecting group Z²⁰⁰.

10

SCHEME 4

SCHEME 4: Esters of formula 17 can be prepared by treating an acid of formula 5 with hydroxysuccinimide in the presence of a coupling agent such as EDC in an inert solvent such as methylene chloride as illustrated in Scheme 4. Treatment of an ester 17 with an amino acid of formula 1 in a solvent such as dioxane, THF or DMF in the presence of a base such as diisopropylethylamine produces 11.

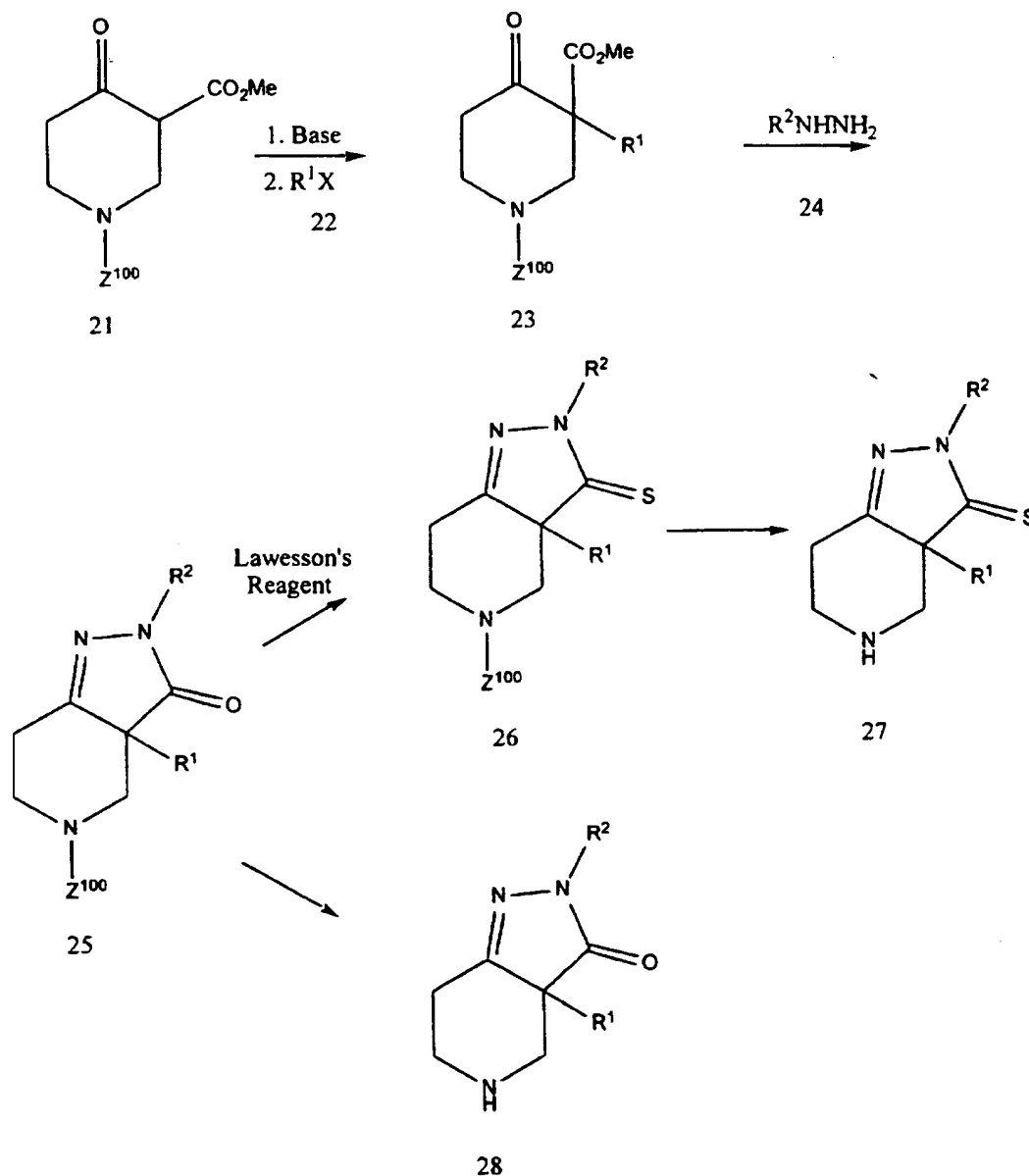
SCHEME 5

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SCHEME 5: As illustrated in Scheme 5, alkylation of the diphenyloxazinone of formula 18 with cinnamyl bromide in the presence of sodium bis(trimethylsilyl)amide generates 19 which is then converted to the desired (D)-2-amino-5-phenylpentanoic acid 20 by removing the protecting group (Prt) and hydrogenation over a PdCl_2

5 catalyst.

SCHEME 6

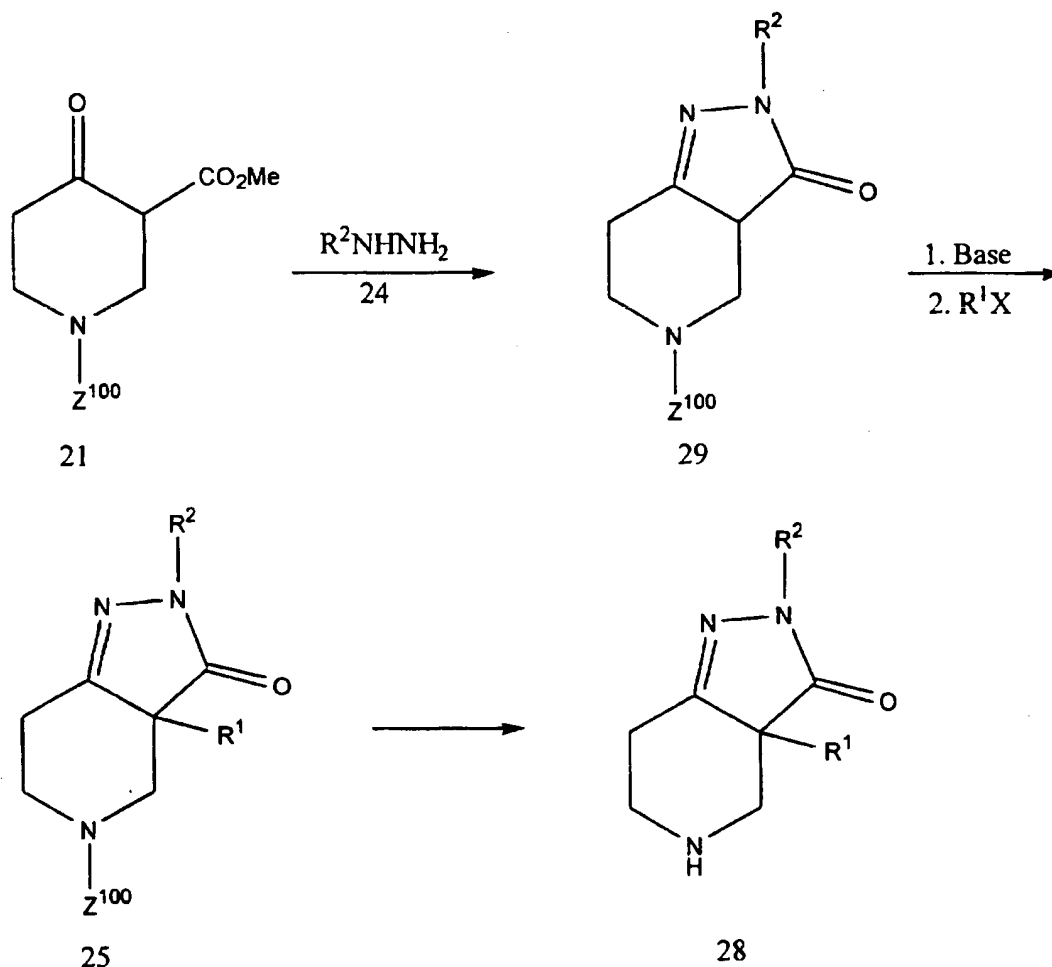


SCHEME 6: Treatment of an ester of formula 21 with a base such as sodium hydride in a solvent such as DMF followed by an alkyl halide 22 generates a

compound of formula 23 as illustrated in Scheme 6. Treating a compound of formula 23 with a hydrazine of formula 24 such as hydrazine or methyl-hydrazine in a solvent such as refluxing ethanol, followed by concentration and heating the residue in toluene at temperatures at or near reflux results in a compound of formula 25.

- 5 Alternatively, 23 can be treated with a salt of a hydrazine in the presence of sodium acetate in refluxing ethanol to give 25. Deprotection of the amine generates a compound of formula 28. Thioamides of formula 26 can be formed by treating 25 with Lawesson's reagent in refluxing toluene or benzene. Removal of the protecting group transforms 26 into 27.

10

SCHEME 7

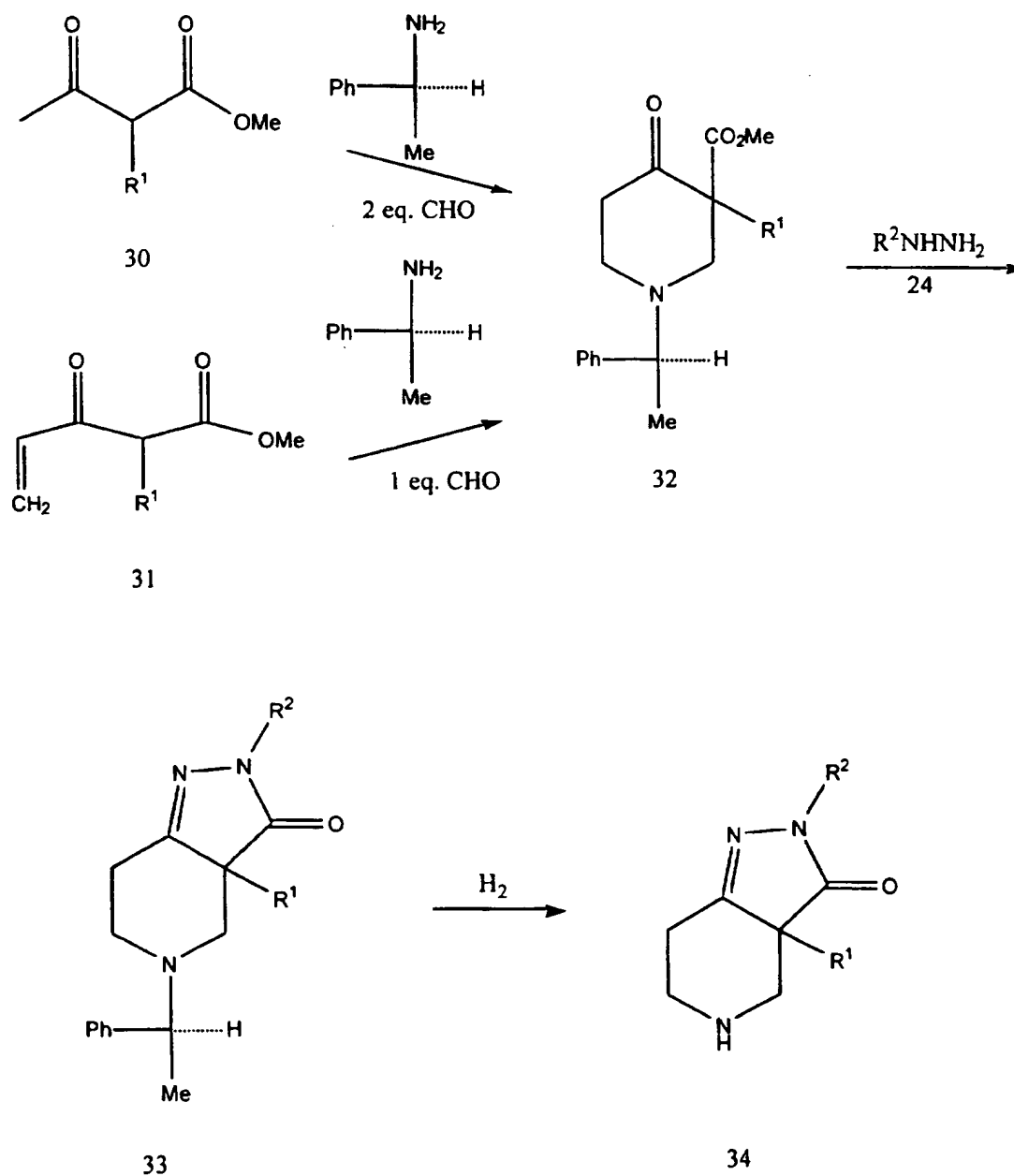
SCHEME 7: Treatment of a compound of formula 21 with a hydrazine of formula 24 in a solvent such as refluxing ethanol, followed by concentration and heating the residue in toluene at temperatures at or near reflux results in compounds of formula

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29. Alternatively, 21 can be treated with a salt of a hydrazine in the presence of sodium acetate in refluxing ethanol to give 29. The amide of formula 29 can be treated with a base such as sodium hydride in a solvent such as DMF followed by an alkyl halide to give 25. Deprotection of the amine generates a compound of formula

5 28.

SCHEME 8

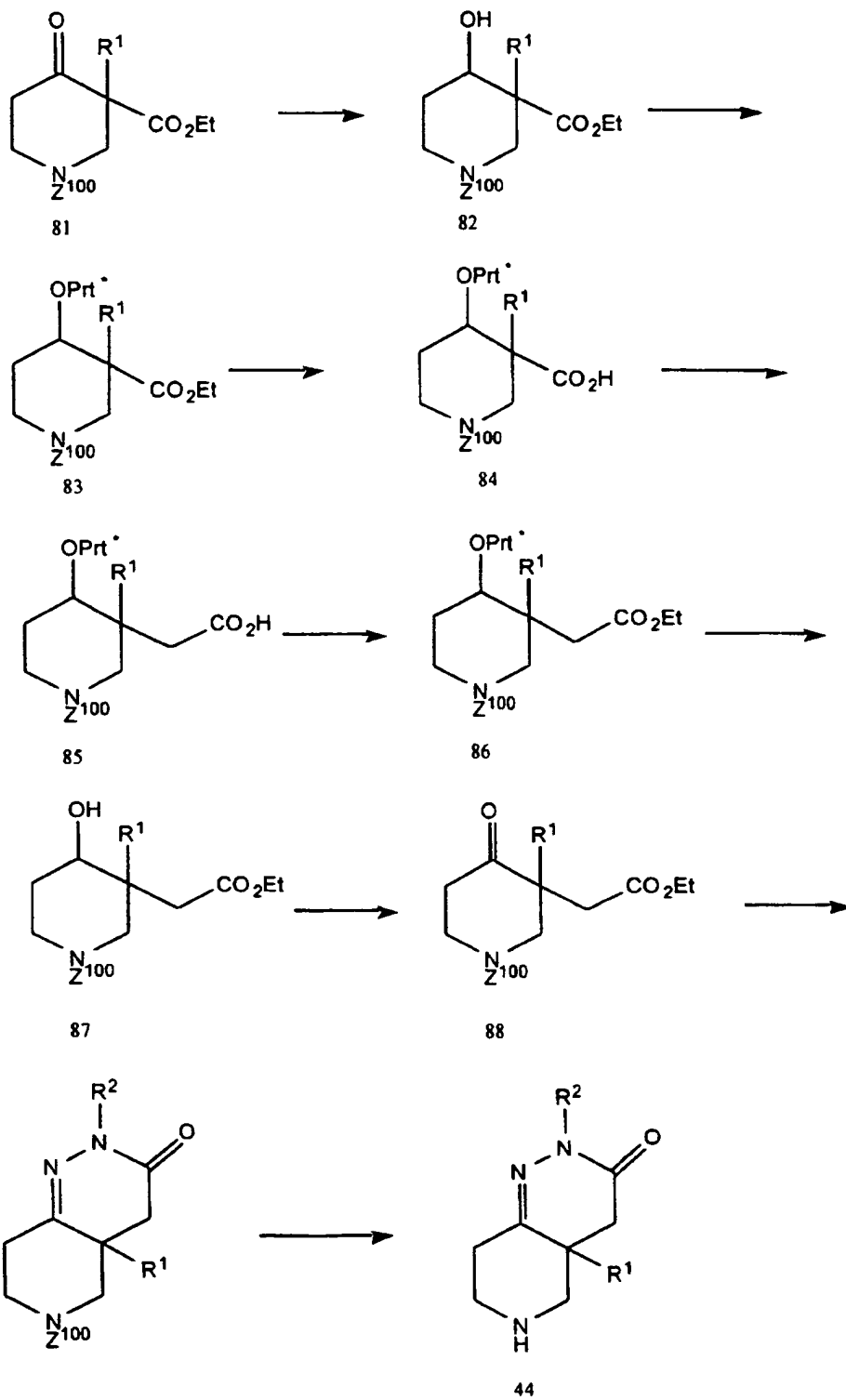


-55-

- SCHEME 8: Reaction of a ketoester of formula 30 with a chiral amine such as alpha-methylbenzylamine with a suitable aldehyde such as formaldehyde, or reaction of a vinyl ketoester of formula 31 with a chiral amine such as alpha-methylbenzylamine with a suitable aldehyde such as formaldehyde, affords a
- 5 compound of formula 32 via a double Mannich reaction. Reaction of 32 with a hydrazine generates a chiral compound of formula 33. Deprotection of the nitrogen with hydrogen and a suitable catalyst such as palladium affords compounds of formula 34.

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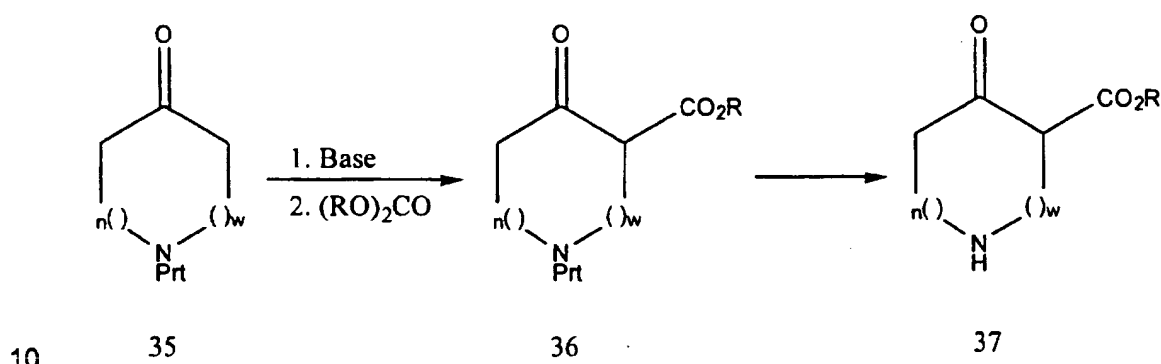
SCHEME 9



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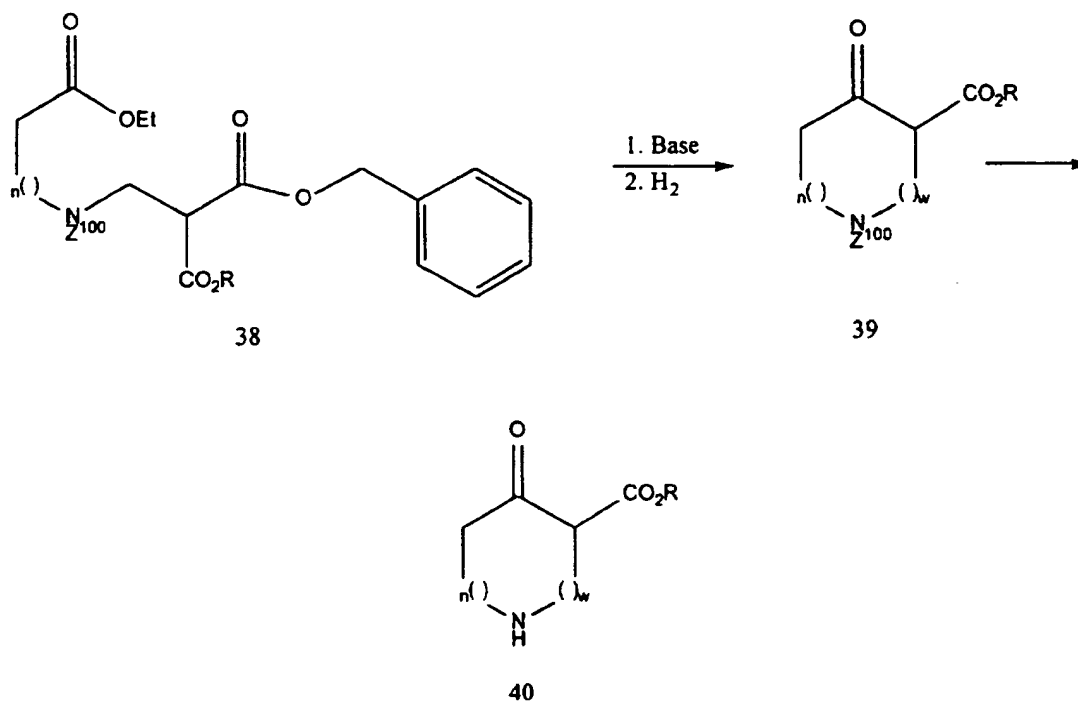
SCHEME 9: Treatment of a compound of formula 81 with a reducing agent such as sodium borohydride and protection of the nitrogen affords a compound of formula 82. Protection of the alcohol affords 83. Saponification of the ester affords a compound of formula 84. Reaction of 84 with thionyl chloride followed by treatment with

5 diazomethane affords the homologated acid of formula 85. Esterification of 85 affords a compound of formula 86, which is O-deprotected to give 87. Oxidation of 87 affords a ketone of formula 88. Reaction of 88 with a hydrazine, followed by nitrogen deprotection affords a compound of formula 44.

SCHEME 10

SCHEME 10: Treatment of a compound of formula 35 with a base such as sodium hydride in a solvent such as DMF followed by treatment with diethylcarbonate generates the ethyl ester of compound 36. Deprotection of the amine transforms 36 into 37.

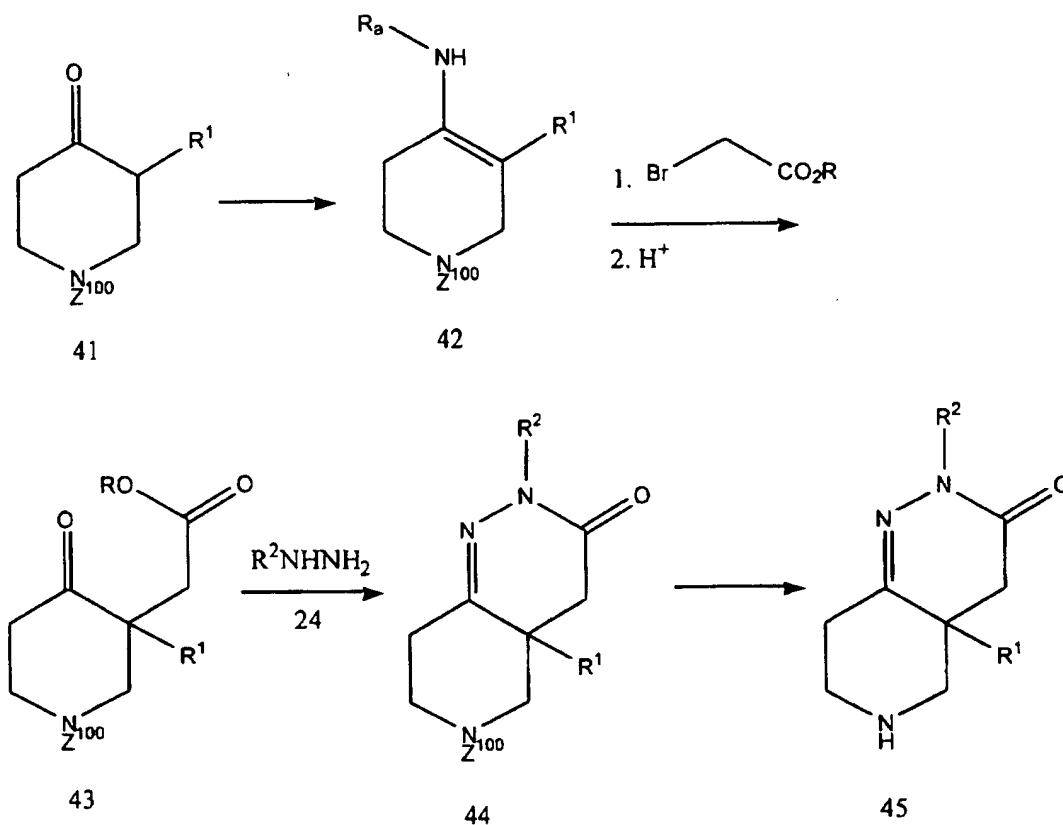
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SCHEME 11

SCHEME 11: Treatment of a malonic ester of formula 38 with a base such as sodium hydride in a solvent such as DMF and subsequent hydrogenolysis of the benzyl group with hydrogen and a catalyst such as palladium in a suitable solvent such as methanol produces the ester of formula 39. Deprotection of the amine generates compounds of formula 40.

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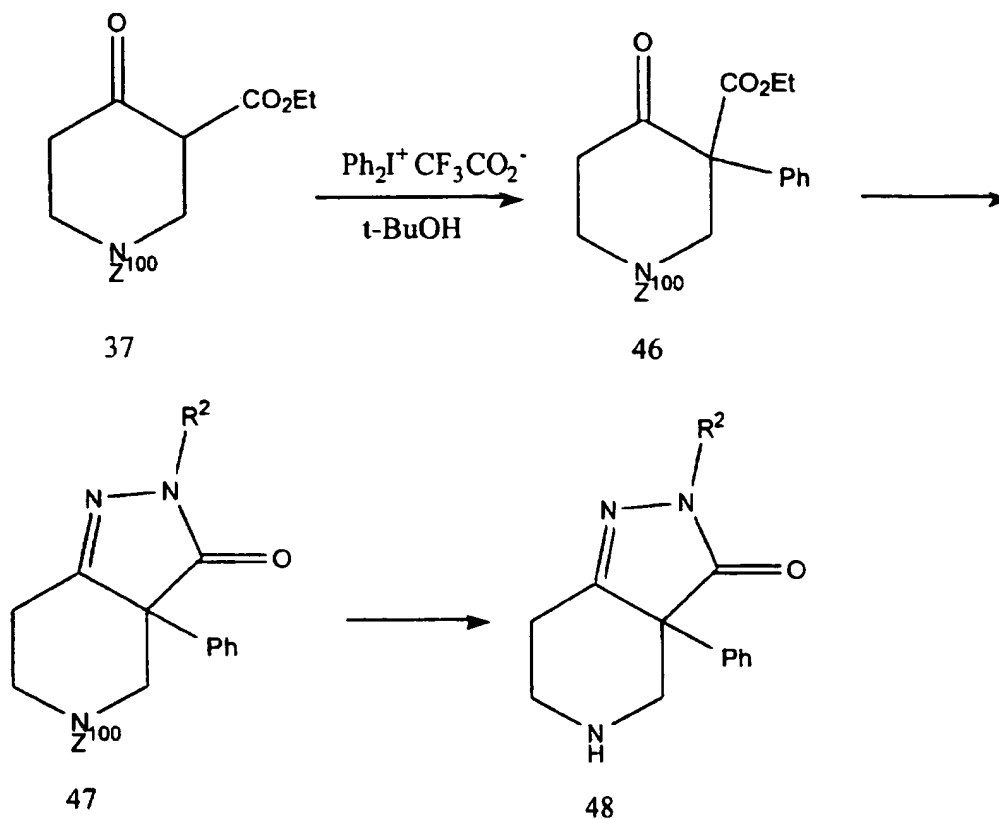
SCHEME 12



- SCHEME 12: Treatment of a ketone of formula 41 with a secondary amine such as piperidine in a suitable solvent such as benzene with removal of water affords an enamine of formula 42. Alkylation of the enamine with an α -haloester such as ethylbromoacetate in a suitable solvent such as benzene or THF using a suitable base such as LDA or $NaN(SiMe_3)_2$ affords a ketoester of formula 43. Reaction with a hydrazine of formula 24 affords the compound of formula 44. Deprotection of the nitrogen affords compounds of formula 45.

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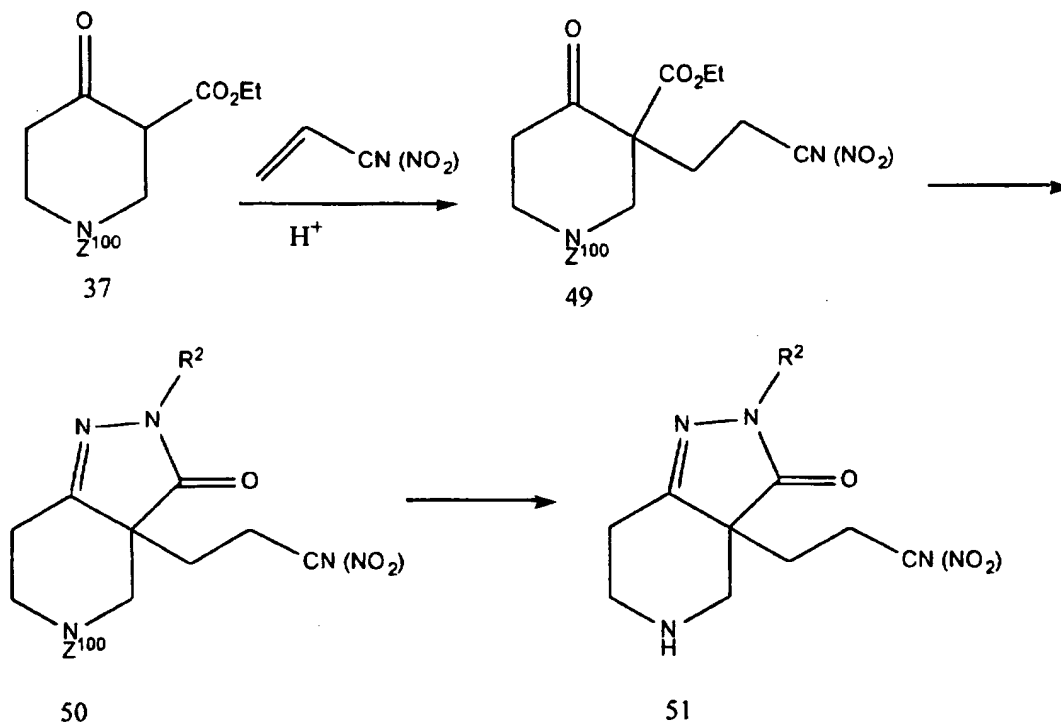
SCHEME 13



Scheme 13: Treatment of a ketoester of formula 37 with an iodonium salt such as diphenyliodonium trifluoroacetate in a suitable solvent such as t-butanol generates a ketoester of formula 46. Reaction of 46 with a hydrazine generates a compound of formula 47. Deprotection of the nitrogen affords compounds of formula 48, see Synthesis, (9), 1984 p. 709 for a detailed description.

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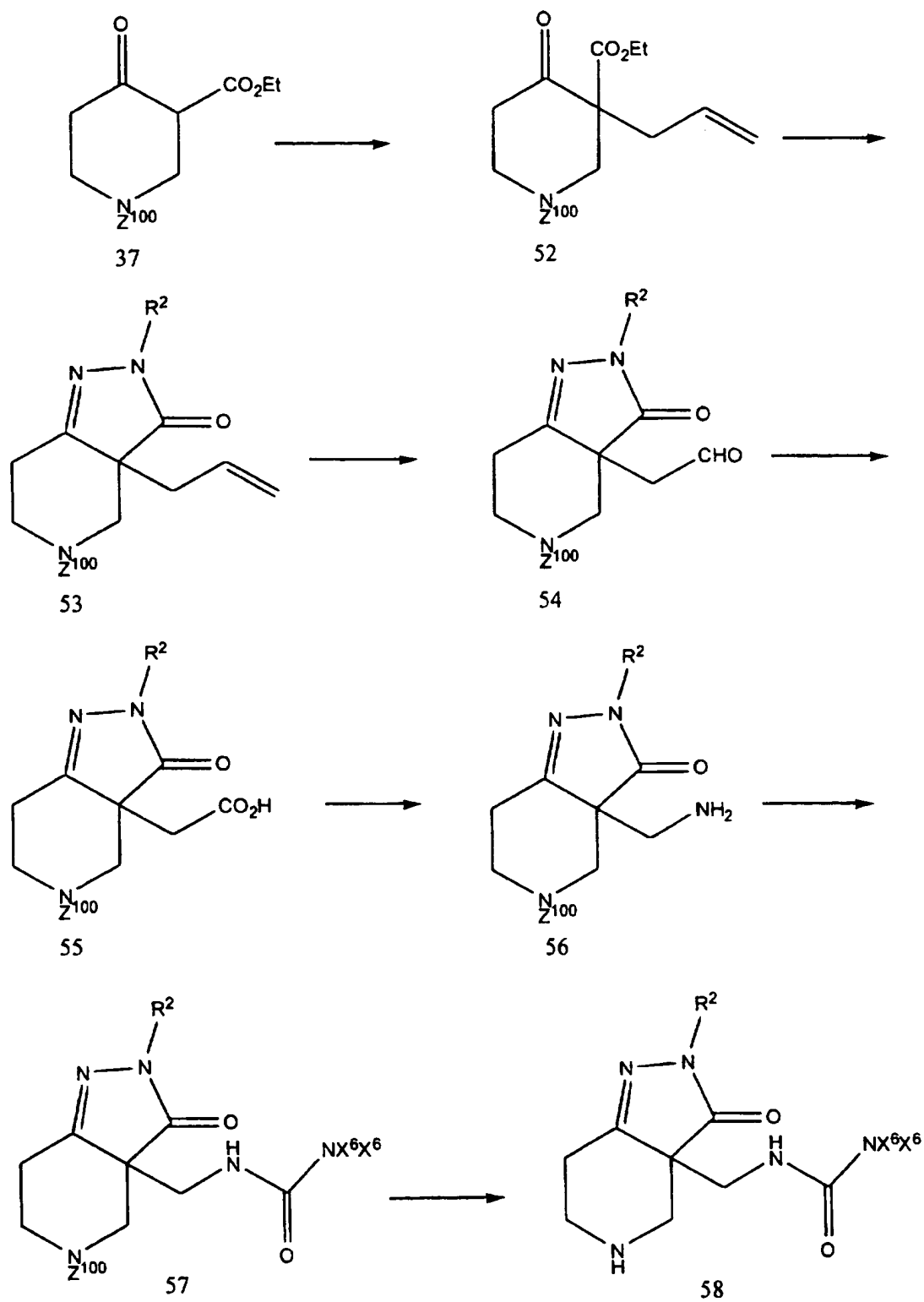
SCHEME 14



SCHEME 14: Treatment of a ketoester of formula 37 with an olefin such as acrylonitrile generates a ketoester of formula 49. Reaction of 49 with a hydrazine
5 generates a compound of formula 50. Deprotection of the nitrogen affords compounds of formula 51.

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SCHEME 15

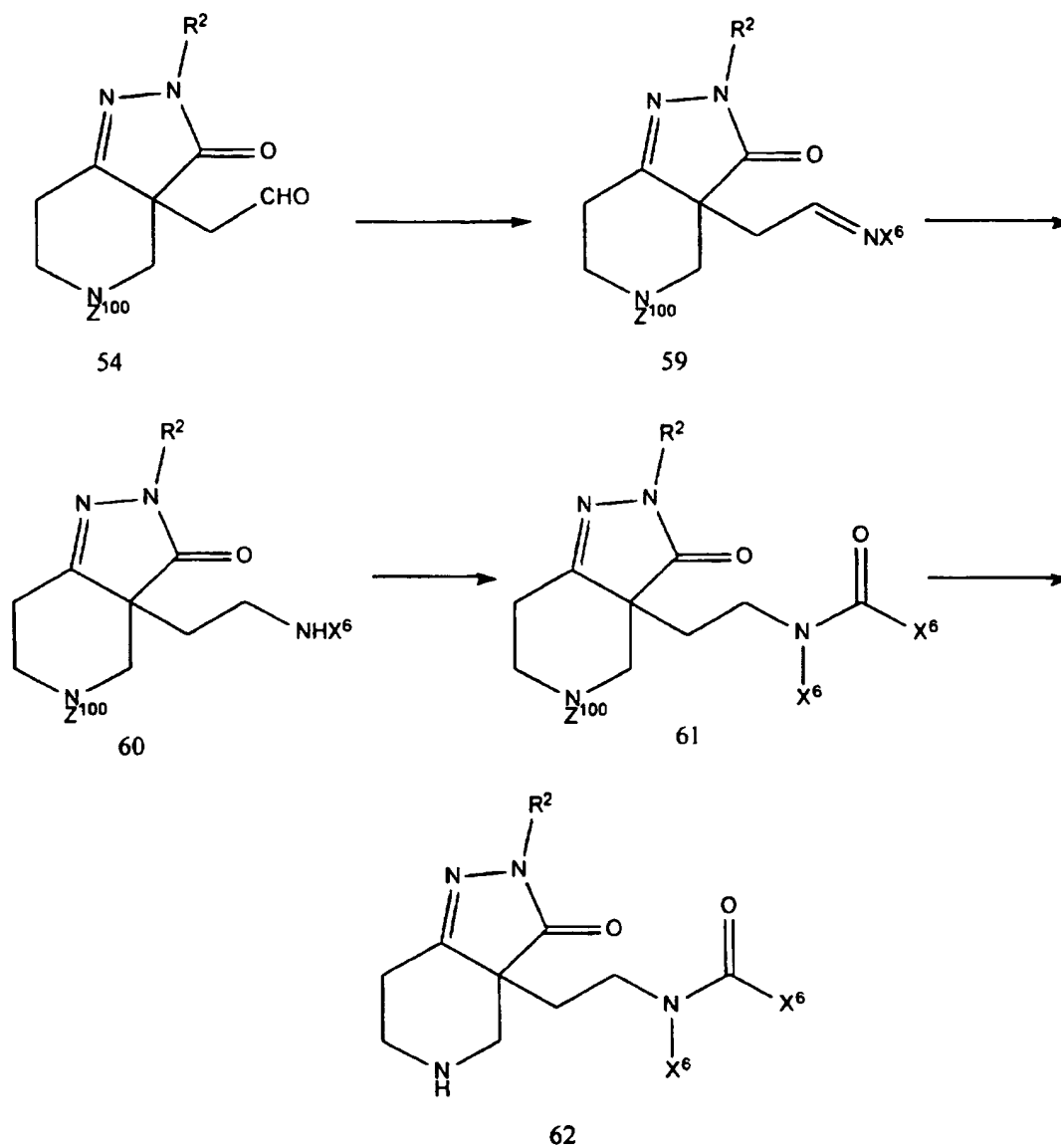


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SCHEME 15: Treatment of a ketoester of formula 37 with allyl bromide and a suitable base such as sodium hydride in a suitable solvent such as DMF affords a ketoester of formula 52. Reaction of 52 with a hydrazine generates a compound of formula 53. Ozonolysis of 53 in a suitable solvent such as methylene chloride
5 followed by treatment with a reducing agent such as dimethylsulfide affords an aldehyde of formula 54. Oxidation of 54 affords a carboxylic acid of formula 55. Curtius rearrangement of 55, followed by hydrolysis of the intermediate isocyanate affords a primary amine of formula 56. Treatment of a compound of formula 56 with an isocyanate or carbamate affords a urea of formula 57. Deprotection of the
10 nitrogen affords compounds of formula 58.

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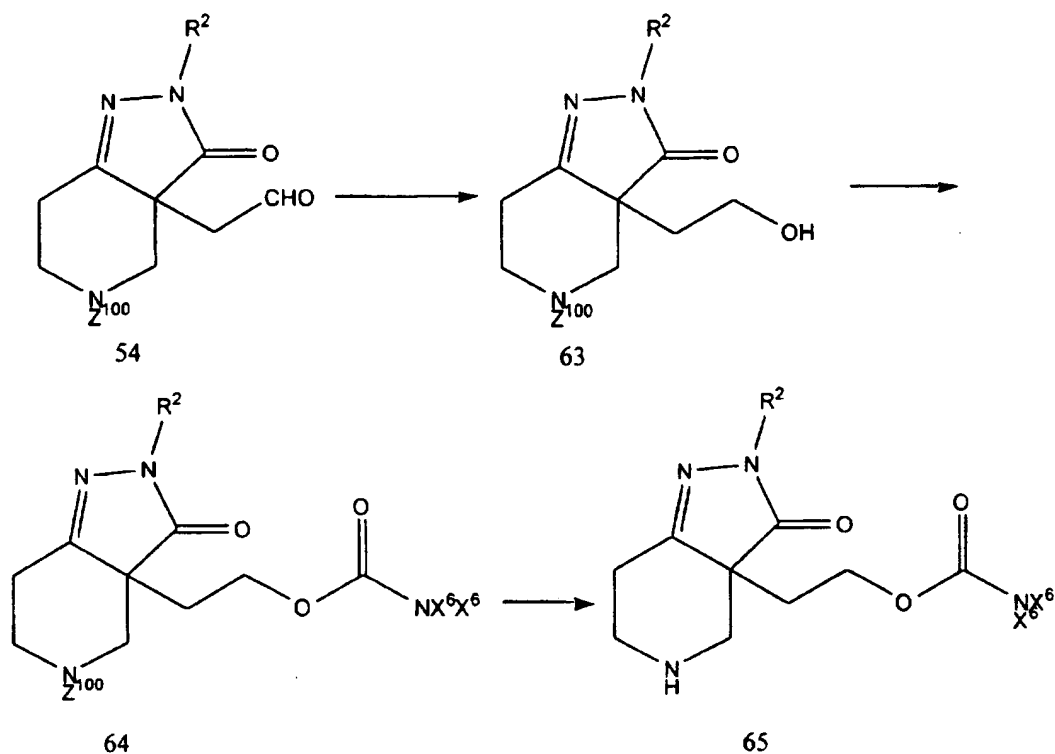
SCHEME 16



SCHEME 16: Treatment of a compound of formula 54 with a primary amine affords an imine of formula 59. Reduction of a compound of formula 59 affords a compound of formula 60. Treatment of a compound of formula 60 with an acylating agent affords a compound of formula 61. Deprotection of the nitrogen affords compounds of formula 62.

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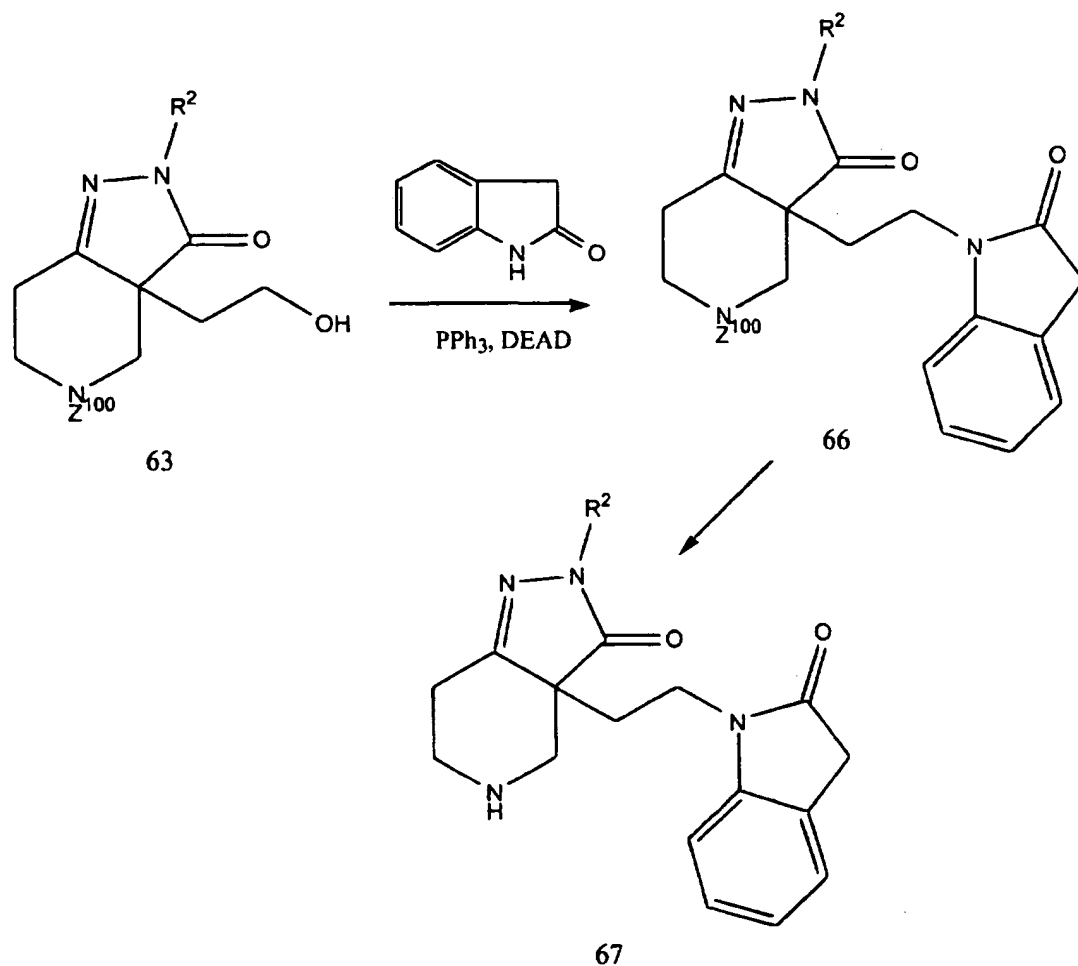
SCHEME 17



SCHEME 17: Treatment of a compound of formula 54 with a reducing agent such as sodium borohydride affords a compound of formula 63. Reaction of 63 with an acylating agent such as an isocyanate or carbamate affords compounds of formula 64. Deprotection of the nitrogen affords compounds of formula 65.

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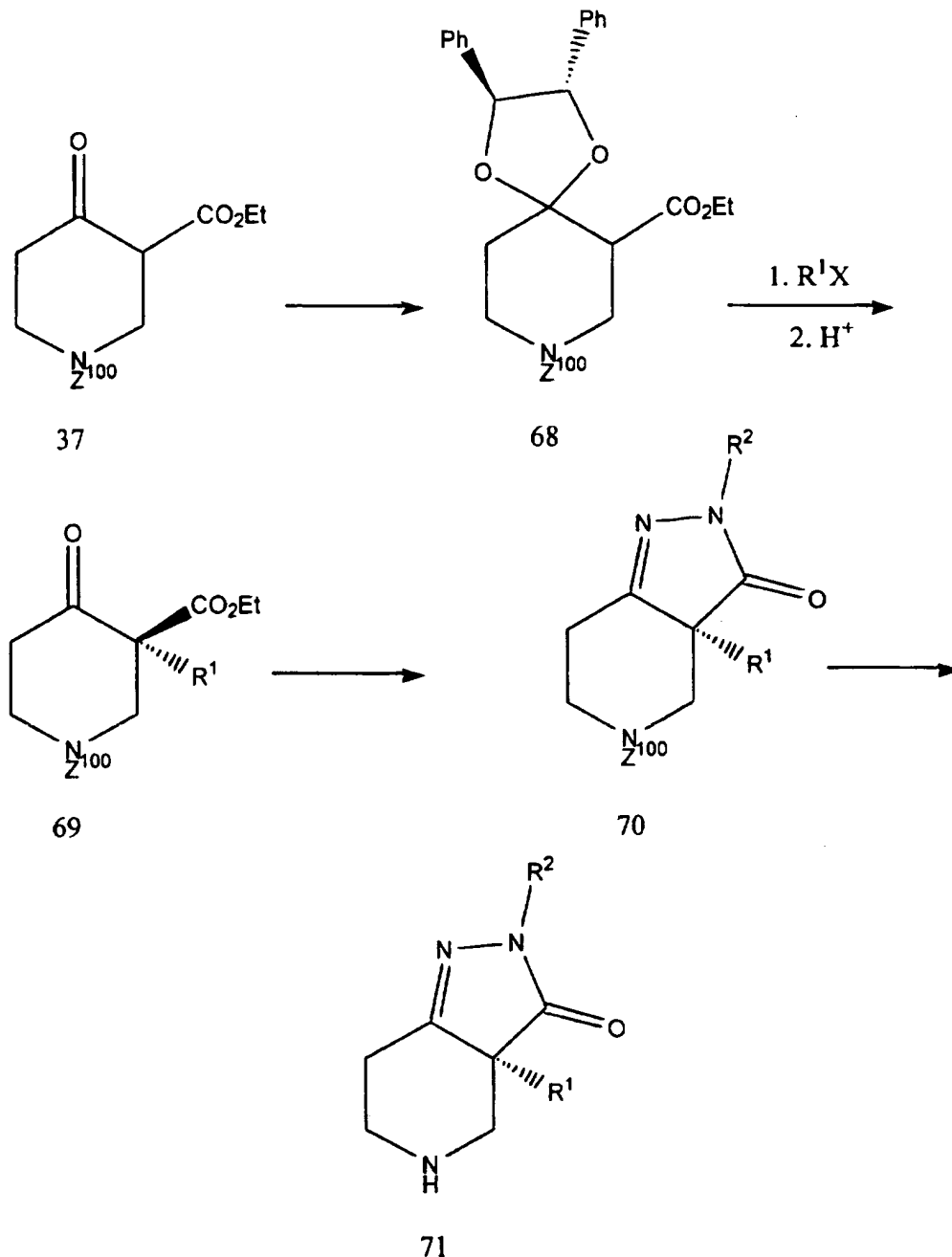
SCHEME 18



5 SCHEME 18: Treatment of a compound of formula 63 with a phosphine such as triphenyl phosphine and an azo compound such as diethylazodicarboxylate and an oxindole affords a compound of formula 66. Deprotection of the nitrogen affords the compound of formula 67.

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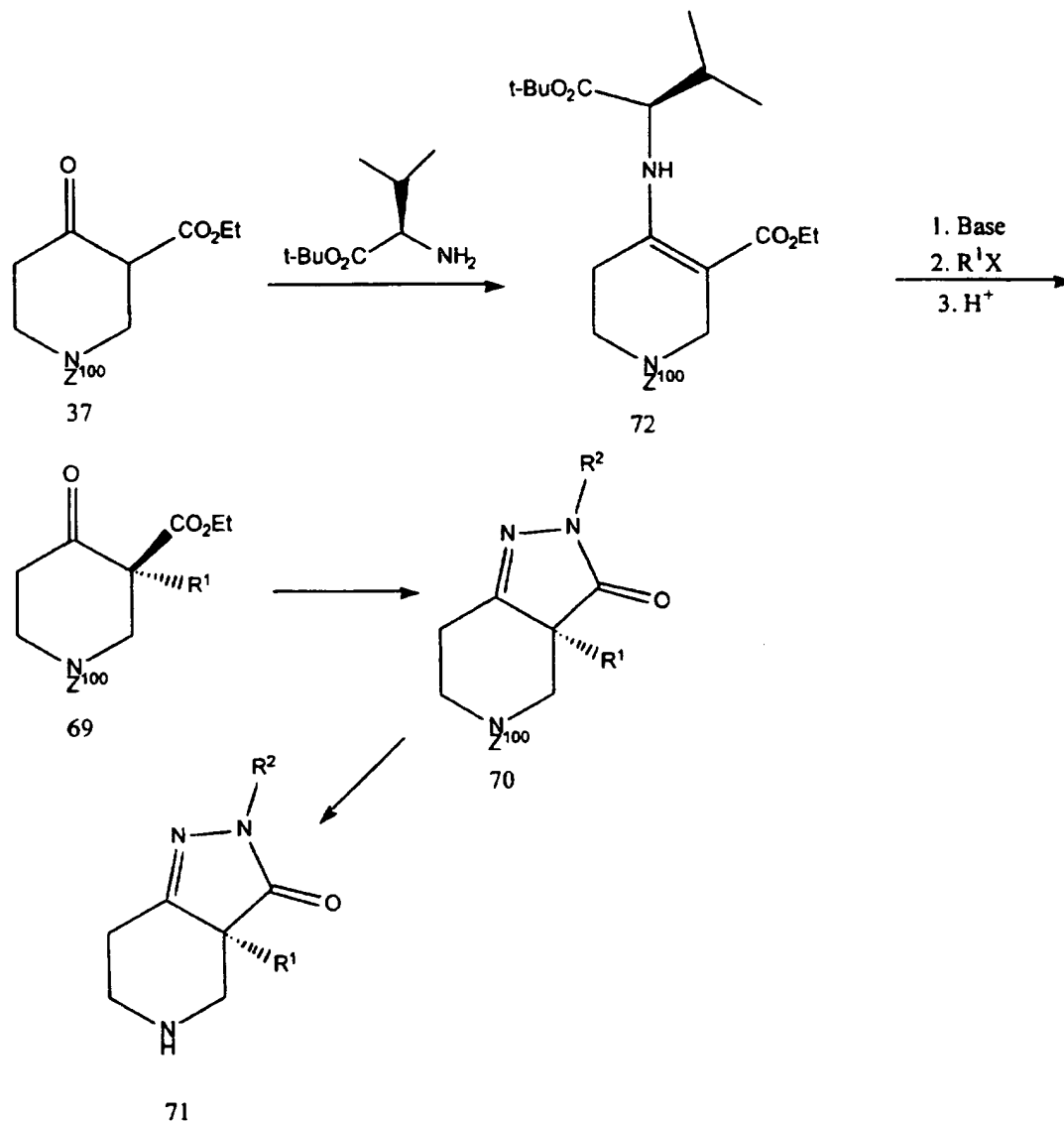
SCHEME 19



SCHEME 19: Treatment of a ketoester of formula 37 with a chiral diol and acid catalyst with removal of water in a suitable solvent such as benzene affords a chiral ketal of formula 68. Alkylation of 68 with an alkyl halide in the presence of a base such as LDA followed by acid-catalyzed hydrolysis of the ketal affords chiral ketoesters of formula 69. Reaction of 69 with a hydrazine generates chiral

-68-

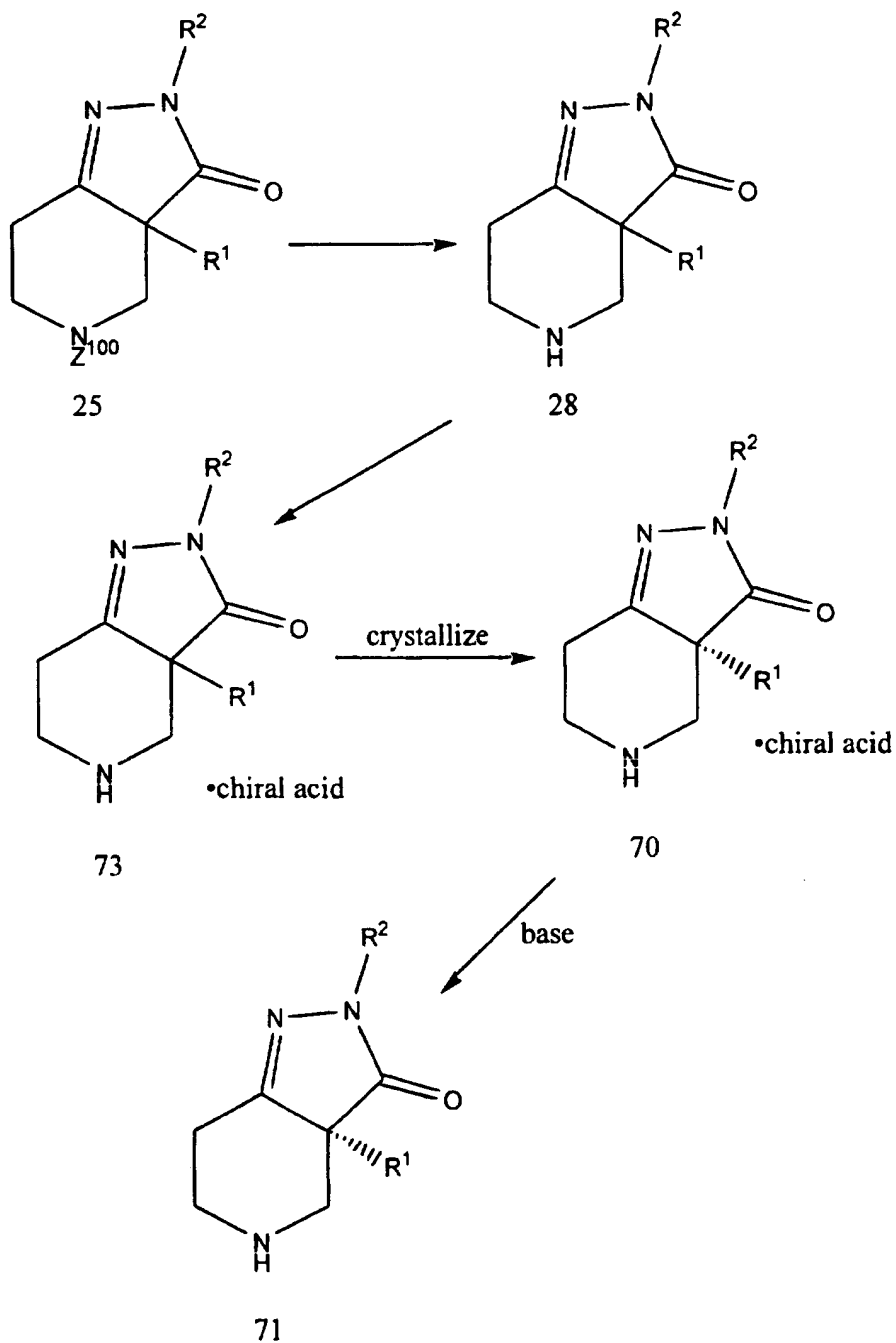
compounds of formula 70. Deprotection of the nitrogen affords compounds of formula 71.

SCHEME 20

- 5 SCHEME 20: Treatment of a ketoester of formula 37 with a chiral amino acid ester such as valine *t*-butyl ester affords a chiral enamine of formula 72. Alkylation of 72 with an alkyl halide in the presence of a base such as LDA followed by acid-catalyzed hydrolysis of the enamine affords chiral ketoesters of formula 69. Reaction of 69 with a hydrazine generates chiral compounds of formula 70.
- 10 Deprotection of the nitrogen affords compounds of formula 71.

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SCHEME 21

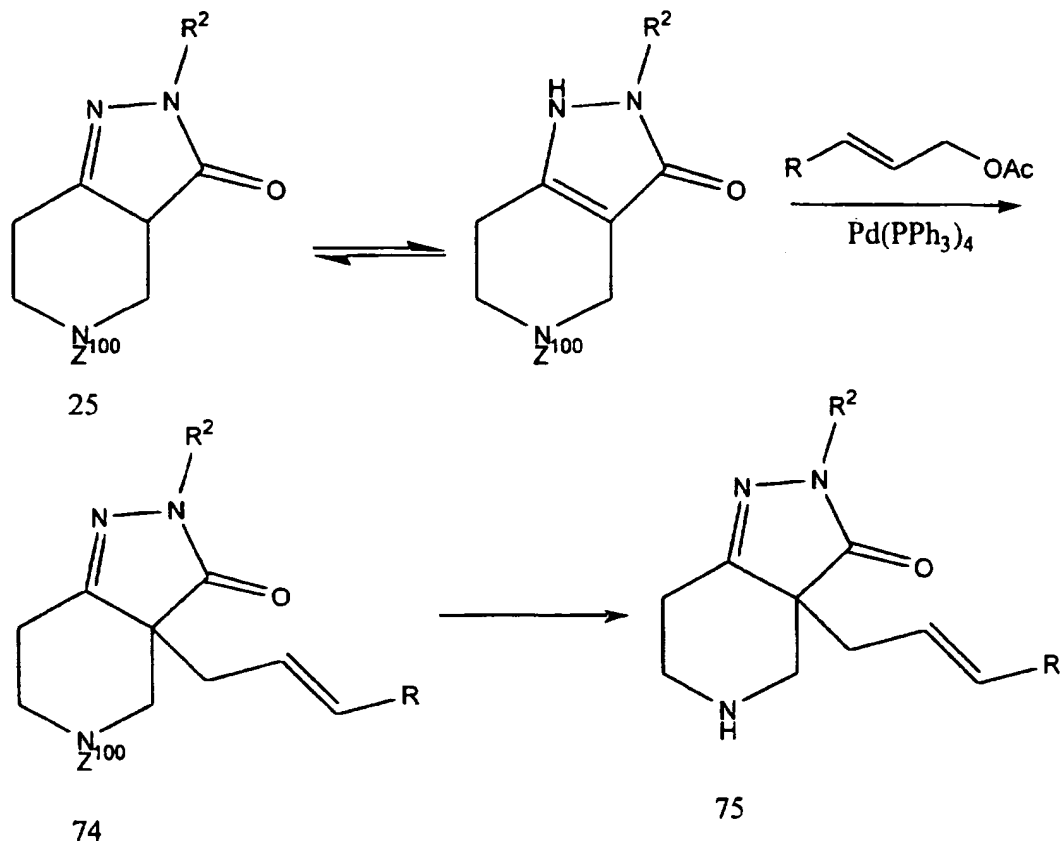


SCHEME 21: Deprotection of the nitrogen of 25 affords compounds of formula 28. Salt formation of 28 with a chiral acid affords a mixture of diastereomeric salts of formula 73. Crystallization of the diastereomeric salts affords the acid salt of chiral

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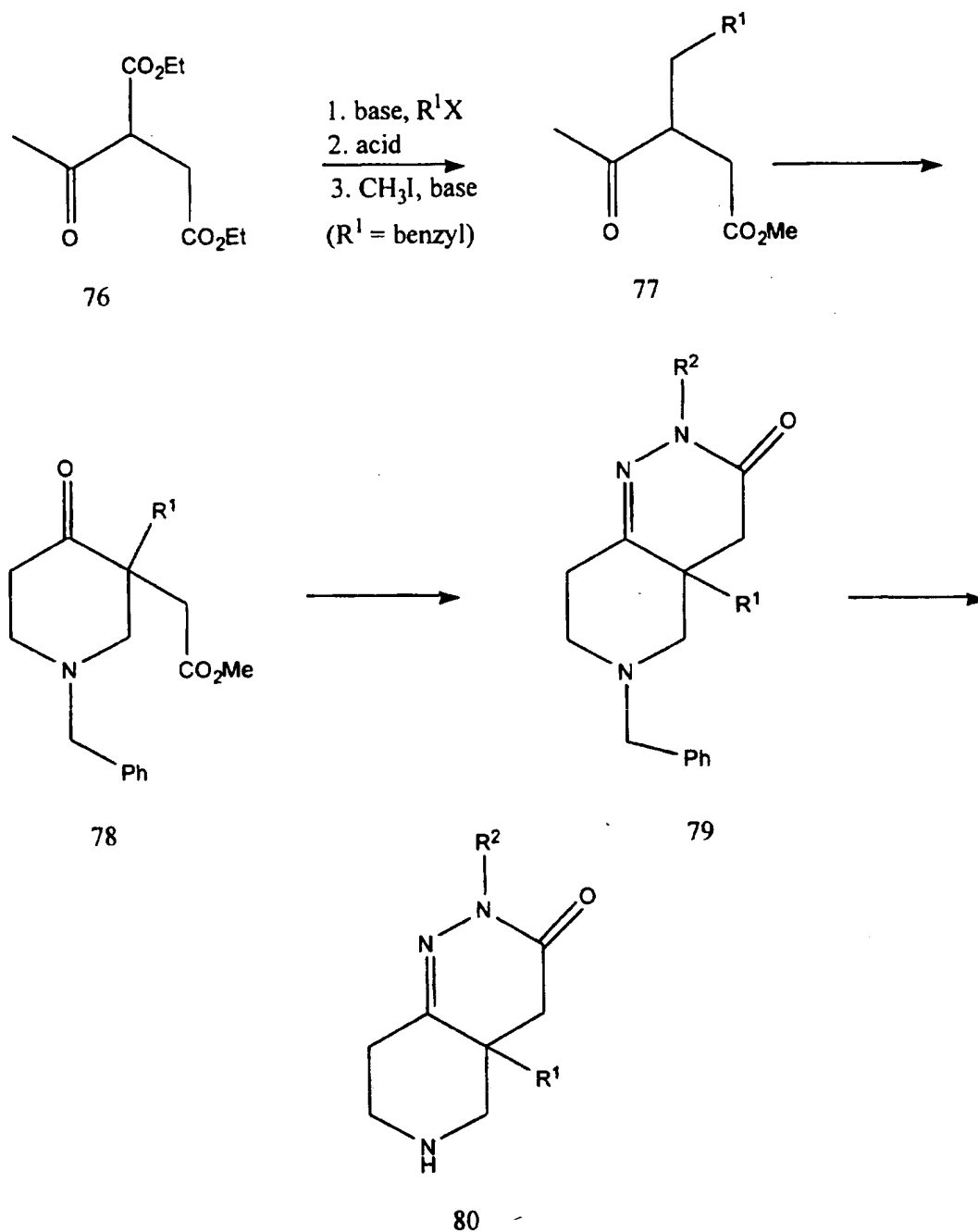
compounds of formula 70. Decomposition of the salt 70 with base liberates chiral compounds of formula 71.

SCHEME 22

- 5 SCHEME 22: Alkylation of compounds of formula 25 with an allylic acetate in the presence of a suitable catalyst such as palladium tetrakis(triphenylphosphine) affords compounds of formula 74. Deprotection of the nitrogen affords compounds of formula 75, see Tetrahedron (50) p. 515, 1994 for a detailed discussion.

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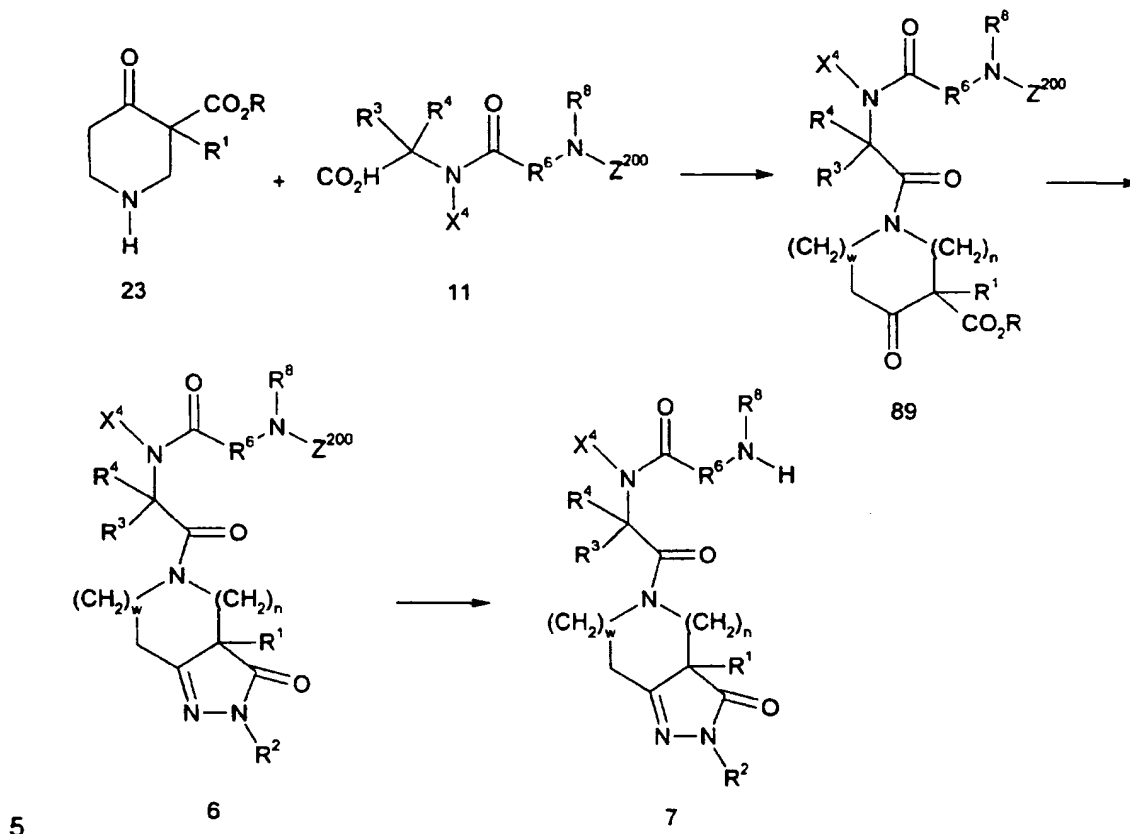
SCHEME 23



SCHEME 23: Treatment of a ketodiester of formula 76 with an alkyl halide in the presence of a base such as sodium hydride followed by acid-catalyzed hydrolysis and decarboxylation, followed by esterification with methyl iodide and a suitable base affords a compound of formula 77. Reaction of a compound of formula 77 with a suitable aldehyde such as formaldehyde and benzylamine affords a compound of

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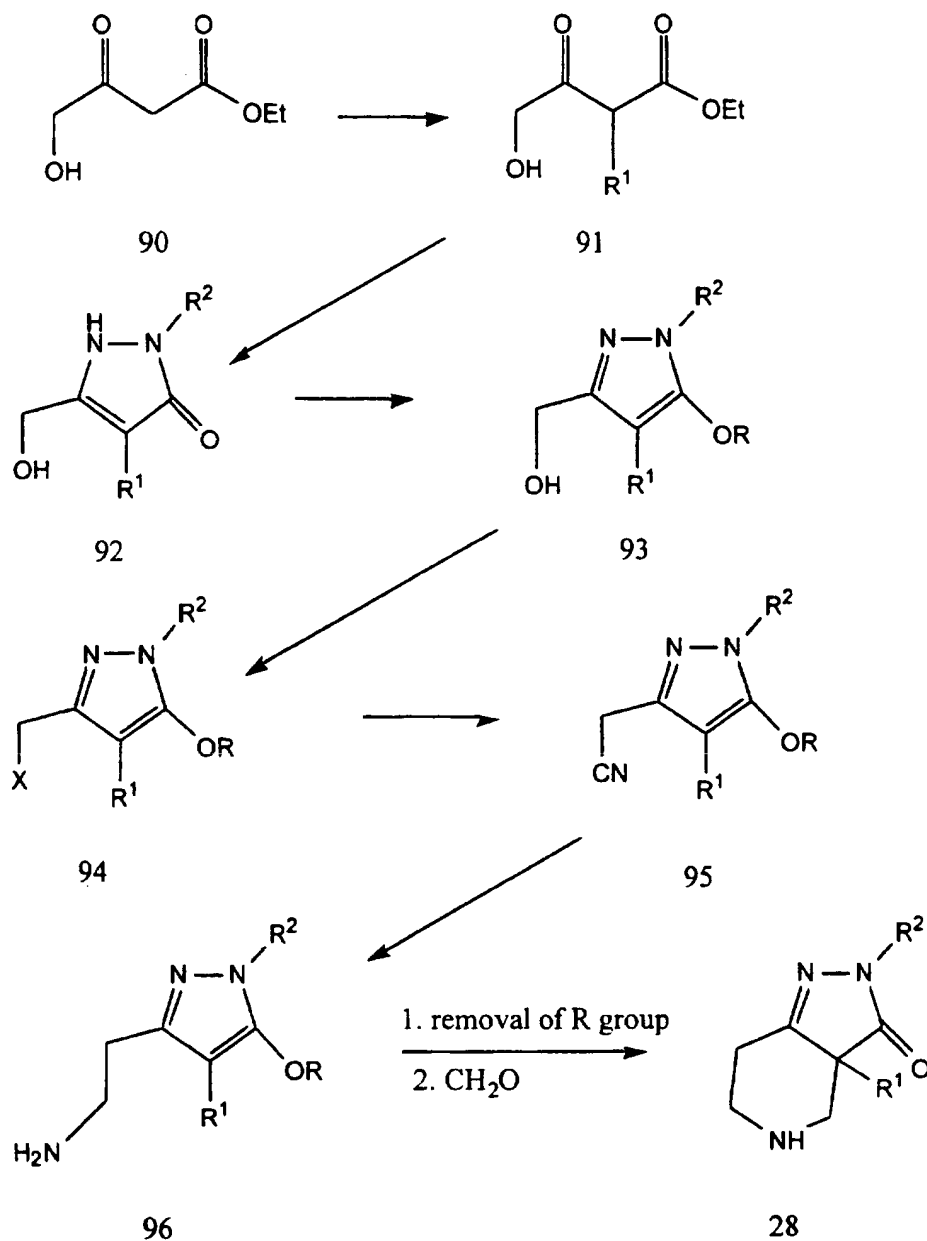
formula 78. Reaction of a compound of formula 78 with a hydrazine generates chiral compounds of formula 79. Deprotection of the nitrogen affords compounds of formula 80.

SCHEME 24

SCHEME 24: Treatment of an amine of formula 23 with an acid of formula 11 in an inert solvent such as dichloromethane or DMF by a coupling reagent such as EDC or DCC in the presence of HOBT affords compounds of formula 89. Reaction of compounds of formula 89 with a hydrazine generates compounds of formula 6. Deprotection of the nitrogen affords compounds of formula 7.

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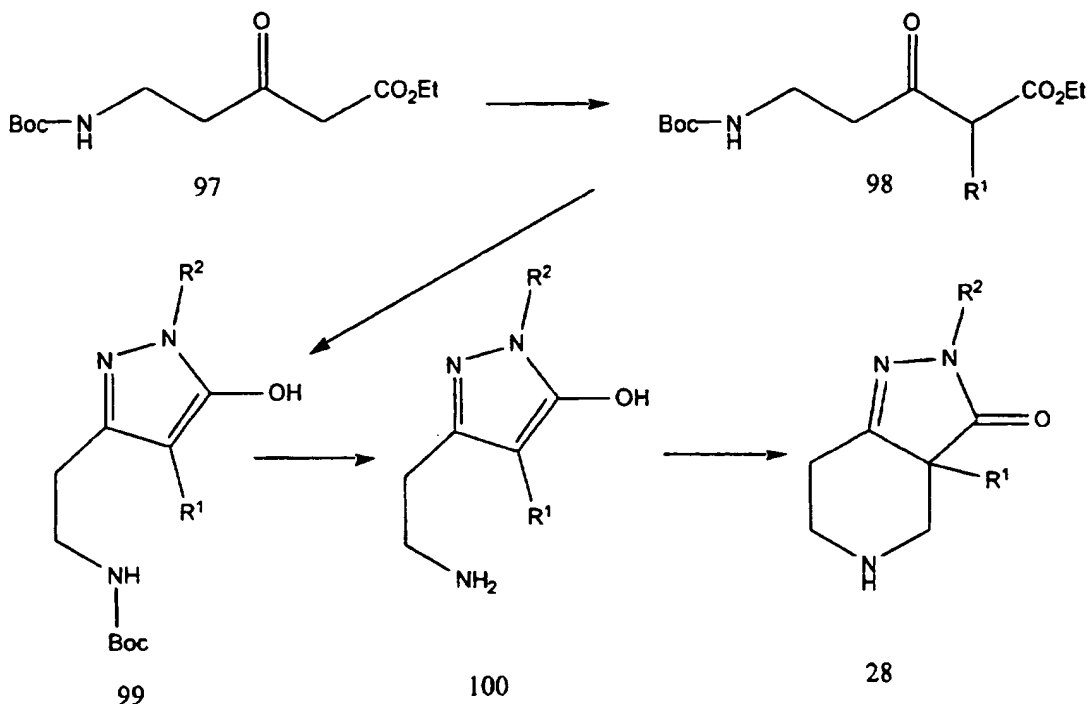
SCHEME 25



5 SCHEME 25: Treatment of a hydroxyacetoacetate ester of formula 90 with an alkyl halide in the presence of a suitable base such as sodium hydride affords compounds of formula 91. Reaction of 91 with a hydrazine generates compounds of formula 92. O-Alkylation of the carbonyl oxygen of 92 affords 93 which is converted to the halide 94. Displacement of the halide X by cyanide ion affords the

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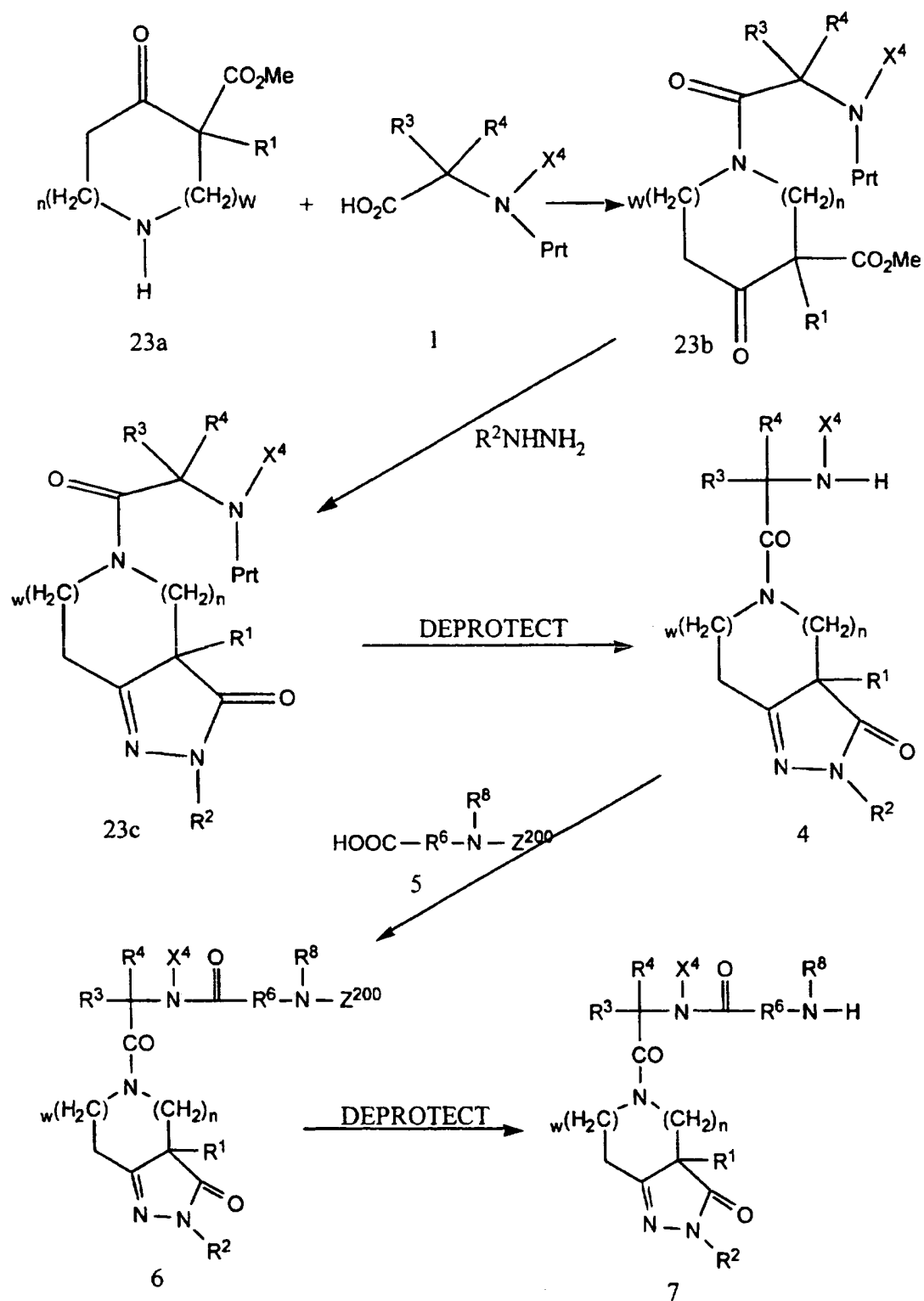
nitrile 95. Reduction of 95 gives the primary amine 96 which is deprotected and cyclized in the presence of formaldehyde to afford 28.

SCHEME 26

- 5 SCHEME 26: Treatment of a beta-keto-protected aminovalerate such as 97 with an alkyl halide in the presence of a suitable base such as sodium hydride affords compounds of formula 98. Reaction of compounds of formula 98 with a hydrazine generates compounds of formula 99. Deprotection of compounds of formula 99 affords primary amines of formula 100. Cyclization of compounds of formula 100 in the presence of formaldehyde affords compounds of formula 28.
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SCHEME 27



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SCHEME 27: Treatment of the amine of formula 23a with an acid such as 1 in the presence of EDC and HOAT in a suitable solvent provides keto-esters of formula 23b. The keto-ester 23b can be treated with a salt of hydrazine in the presence of sodium acetate in refluxing ethanol to give hydrazines of formula 23c. Deprotection under suitable conditions gives amines of formula 4. Coupling of intermediates of formula 4 to amino acids of formula 5 can be effected as described above to give intermediates of formula 6. Deprotection of amine 6 affords compounds of formula 7.

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention.

General Experimental Procedures:

Amicon silica 30 μ M, 60 Å pore size, was used for column chromatography. Melting points were taken on a Buchi 510 apparatus and are uncorrected. Proton and carbon NMR spectra were recorded on a Varian XL-300, Bruker AC-300, Varian Unity 400 or Bruker AC-250 at 25 °C. Chemical shifts are expressed in parts per million down field from trimethylsilane. Particle beam mass spectra were obtained on a Hewlett-Packard 5989A spectrometer using ammonia as the source of chemical ionization. For initial sample dissolution, chloroform or methanol was employed. Liquid secondary ion mass spectra (LSIMS) were obtained on a Kratos Concept-1S high resolution spectrometer using cesium ion bombardment on a sample dissolved in a 1:5 mixture of dithioerythritol and dithiothreitol or in a thioglycerol matrix. For initial sample dissolution chloroform or methanol was employed. Reported data are sums of 3-20 scans calibrated against cesium iodide. TLC analyses were performed using E. Merck Kieselgel 60 F254 silica plates visualized (after elution with the indicated solvent(s)) by staining with 15% ethanolic phosphomolybdic acid and heating on a hot plate.

General Procedure A (Peptide coupling using EDC): A 0.2-0.5 M solution of the primary amine (1.0 equivalent) in dichloromethane (or a primary amine hydrochloride and 1.0-1.3 equivalents of triethylamine) is treated sequentially with 1.0-1.2 equivalents of the carboxylic acid coupling partner, 1.5-1.8 equivalents hydroxybenzotriazole hydrate (HOBt) or HOAT and 1.0-1.2 equivalents (stoichiometrically equivalent to the quantity of carboxylic acid) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and the mixture is

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stirred overnight in an ice bath (the ice bath is allowed to warm, thus the reaction mixture is typically held at about 0-20 °C for about 4-6 h and about 20-25 °C for the remaining period). The mixture is diluted with ethyl acetate or other solvent as specified, and the resulting mixture washed twice with 1N NaOH, twice with 1N HCl
5 (if the product is not basic), once with brine, dried over Na₂SO₄, and concentrated giving the crude product which is purified as specified. The carboxylic acid component can be used as the dicyclohexylamine salt in coupling to the primary amine or hydrochloride of the latter; in this case no triethylamine is employed.

Example 1

10 2-Amino-N-{1(R)-benzyloxymethyl-2-[3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide hydrochloride and

2-Amino-N-{1(R)-benzyloxymethyl-2-[3a-(S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide hydrochloride
15

A. 4-Oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

A mixture of 8.00 g (38.5 mmol) of 4-oxo-piperidine-3-carboxylic acid ethyl ester hydrochloride, 9.23 g (42.4 mmol) of di-tert-butylidicarbonate, and 3.89 g (38.5 mmol) of triethylamine in 150 mL of THF was stirred at room temperature for about 72 h.

20 The mixture was concentrated and the residue was dissolved in ethyl acetate and washed three times each with 10% aqueous HCl, saturated aqueous sodium bicarbonate solution, and brine, dried over MgSO₄, and concentrated to give 10.0 g of **1A** as a white solid. MS (Cl, NH₃) 272 (MH⁺).

B. 3-(R,S)-(4-Fluoro-benzyl)-4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester
25

To a solution of 2.00 g (7.4 mmol) **1A** in 10 mL of DMF was added 282 mg (7.4 mmol) of sodium hydride (60% oil dispersion) and the mixture was stirred at room temperature for about 15 min. A solution of 1.39 g (7.4 mmol) 4-fluorobenzyl bromide in 7 mL of DMF was added to the stirring solution and the mixture was
30 stirred for about 72 h at room temperature. The mixture was diluted with ethyl acetate and washed once with water and four times with brine, dried over MgSO₄, and concentrated to give 2.8 g of **1B**. MS (Cl, NH₃) 380 (MH⁺).

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C. 3a-(R,S)-(4-Fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 2.54 g (6.7 mmol) of **1B** and 309 mg (6.7 mmol) of methylhydrazine in 100 mL of ethanol was heated at reflux for about 8 h. The mixture was concentrated and the residue was dissolved in 100 mL toluene and heated at reflux for about 17 h. The mixture was concentrated and the residue was purified by silica gel chromatography using an elution gradient of (18:82 v/v ethyl acetate:hexane) to (75:25 v/v ethyl acetate:hexane) to give 1.0 g of **1C** as a clear colorless oil. MS (Cl, NH₃) 362 (MH⁺).

10 D. 3a-(R,S)-(4-Fluoro-benzyl)-2-methyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one trifluoroacetate

To 1.00 g (2.8 mmol) of **1C** was added 10 mL of trifluoroacetic acid at about 0 °C and the mixture was stirred for about 1 h. Ethyl acetate was added and the mixture was concentrated to give 1.0 g of **1D**. MS (Cl, NH₃) 263 (MH⁺).

15 E. (R)-3-Benzoyloxy-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionic acid

To 1.83 g (6.2 mmol) of N-t-BOC-O-benzyl-D-serine in 35 mL of DMF was added 1.02g (7.4 mmol) of potassium carbonate followed by 0.92g (6.5 mmol) of iodomethane. The mixture was stirred overnight at about 24 °C under an atmosphere of nitrogen. The reaction mixture was diluted with 200 mL of water, and extracted three times with ethyl acetate. The combined organics were washed five times with water and once with brine, dried over MgSO₄ and concentrated. The crude (R)-3-benzoyloxy-2-tert-butoxycarbonyl-amino-propionic acid methyl ester was dissolved in 15 mL of cold trifluoroacetic acid at about 0 °C and the mixture was stirred for about 2 h. The mixture was concentrated and the residue was diluted with 1N NaOH and extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄ to give 0.84 g (4.02 mmol) of the resulting (R)-2-amino-3-benzoyloxy-propionic acid methyl ester which was coupled to 0.81 g (4.02 mmol) of N-t-BOC- α -methylalanine to give 1.80 g of (R)-3-benzoyloxy-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionic acid methyl ester. The crude product was dissolved in 20 mL of 4:1 THF:water and a solution of 335 mg (7.98 mmol) of lithium hydroxide hydrate in 1 mL of water was

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added to the solution and the mixture was stirred overnight at room temperature. The mixture was concentrated and the residue was diluted with ethyl acetate and acidified with aqueous HCl and extracted three times with ethyl acetate. The organic extracts were combined and washed once with brine, dried over Na₂SO₄ and

5 concentrated to give 1.60 g of **1E** as an oil which solidified on standing. ¹H NMR (CDCl₃ 300 MHz) δ 7.30 (m, 5H), 7.10 (d, 1H), 5.07 (bs, 1H), 4.68 (m, 1H), 4.53 (q, 2H) 4.09 (m, 1H), 3.68 (m, 1H), 1.3-1.5 (m, 15H).

F. (1-{1(R)-Benzyloxymethyl-2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethylcarbamoyl}-1-methyl-ethyl)-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 193 mg (0.51 mmol) of **1D** and 196 mg (0.51 mmol) of **1E** were coupled to give a mixture of diastereomers. The residue was purified by silica gel chromatography using an elution gradient of (1:1 v/v ethyl acetate:hexane) to 100% ethyl acetate to give 60 mg of less polar **1F** isomer **1** and 100 mg of more polar **1F** isomer **2**. MS (CI, NH₃) 624 (MH⁺) for both isomers.

G. 2-Amino-N-{1(R)-benzyloxymethyl-2-[3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide hydrochloride

20 To 60 mg (0.10 mmol) of **1F** isomer **1** in 10 mL of ethanol was added 4 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h. The mixture was concentrated and the residue was precipitated from ethanol/hexane to give 50 mg of **1G** isomer **1** as a white powder. MS (CI, NH₃) 524 (MH⁺). ¹H NMR (CD₃OD): (partial) δ 7.32 (m, 5 H), 7.12 (m, 2 H), 6.91 (m, 2 H), 5.15 (m, 1 H), 4.54 (s, 2 H), 3.78 (m, 2 H) 3.02 (m, 7 H), 2.66 (m, 2 H), 1.57 (s, 6 H).

H. 2-Amino-N-{1(R)-benzyloxymethyl-2-[3a-(S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide hydrochloride

To 100 mg (0.16 mmol) of **1F** isomer **2** in 10 mL of ethanol was added 4 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h. The mixture was concentrated and the residue was precipitated from ethanol/hexane

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to give 60 mg of 1H isomer 2 as a white powder. MS (Cl, NH₃) 524 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.32 (m, 5 H), 7.08 (m, 2 H), 6.95 (m, 2 H), 6.80 (m, 2 H), 5.30 (m, 1 H), 4.61 (m, 3 H), 3.80 (m, 2 H), 2.58 (m, 3 H), 1.58 (s, 6 H).

Example 2

5 2-Amino-N-[2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

A. (R)-2-Amino-3-[(1H-indol-3-yl)-propionic acid methyl ester]

To 4.92 g (16.2 mmol) of N-α-t-BOC-D-tryptophan in 100mL of DMF was added 2.46
10 g (17.8 mmol) of potassium carbonate followed by 2.41 g (17.0 mmol) of iodomethane, and the mixture was stirred overnight at 24°C under an atmosphere of nitrogen. The reaction mixture was diluted with water, and extracted three times with ethyl acetate. The combined organics were washed five times with 500 mL of water and once with brine, dried over MgSO₄ and concentrated to give 4.67 g of a white
15 solid. To the crude (R)-2-tert-butoxycarbonylamino-3-(1H-indol-3-yl)-propionic acid methyl ester was added 15 mL of cold trifluoroacetic acid at about 0 °C and the mixture was stirred for about 2 h. The mixture was concentrated and the residue was diluted with 1N NaOH and extracted three times with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄ to give
20 (R)-2-amino-3-(1H-indol-3-yl)-propionic acid methyl ester as an orange oil in quantitative yield.

B. (R)-2-(2-tert-Butoxycarbonylamino-2-methyl-propionylamino)-3-(1H-indol-3-yl)-propionic acid methyl ester.

The crude product from 2A 1.55 g (7.1 mmol) was coupled to 1.44 g (7.1 mmol) of
25 N-t-BOC-α-methylalanine according to Procedure A to give an oil which was purified by silica gel chromatography using a gradient of 10%, 20%, 30%, 40% and 50% ethyl acetate in hexane to elute. Recovered 1.32 g of (R)-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-3-(1H-indol-3-yl)-propionic acid methyl ester.

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C. (R)-2-(2-tert-Butoxycarbonylamino-2-methyl-propionylamino)-3-(1H-indol-3-yl)-propionic acid

To a solution of 1.03 g (2.64 mmol) of 2B in 10 mL of THF was added 381 mg (9.1 mmol) of lithium hydroxide hydrate in 2 mL of water and the mixture was stirred
5 overnight at room temperature. Excess THF was removed by evaporation, and the basic aqueous mixture was extracted three times with ethyl acetate, and then acidified to pH 4 with dilute acetic or hydrochloric acid. The product was extracted with ethyl acetate and the combined organic extracts were washed with brine, dried over MgSO₄ and evaporated to give 1.03 g of 2C as an orange foam. MS (CI, NH₃)
10 390 (MH⁺). ¹H NMR (CDCl₃ 300 MHz) δ 7.61 (d, 1H), 7.48 (d, 1H), 7.27 (t, 1H), 7.10 (t, 1H), 4.81 (bs, 1H), 3.35 (m, 1H), 1.49 (s, 6H), 1.32 (s, 9H).

D. {1-[2-[3a-(R,S)-(4-Fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

15 According to the method outlined in General Procedure A, 193 mg (0.51 mmol) of 1D and 200 mg (0.51 mmol) of 2C were coupled and the residue was purified by silica gel chromatography using an elution gradient of (1:1 v/v ethyl acetate:hexane) to 100% ethyl acetate to give 230 mg of 2D. MS (CI, NH₃) 633 (MH⁺).

E. 2-Amino-N-[2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

To 230 mg (0.36 mmol) of 2D in 10 mL of ethanol was added 4 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h. The mixture was concentrated and the residue was precipitated from ethanol/hexane to give 130 mg
25 of 2E as a white powder. MS (CI, NH₃) 533 (MH⁺). ¹H NMR (CD₃OD): (partial) δ 7.79 (d, 1 H), 7.48 (m, 1 H), 7.33 (m, 2 H), 7.19 - 6.77 (m, 7 H), 6.54 (m, 1 H), 5.17 (m, 1 H), 4.02 (m, 1 H), 3.11 - 2.68 (m, 6 H), 2.47 (m, 2 H), 2.03 (m, 2 H), 1.59 (m, 6 H).

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Example 3

2-Amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide

A. 4-Oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

- 5 To a mixture of 7.00 g (36.2 mmol) of 4-oxo-piperidine-3-carboxylic acid methyl ester and 8.82 g (72.3 mmol) of 4,4-dimethylaminopyridine in 200 mL of methylene chloride at about 0 °C was added a solution of 7.88 g (36.2 mmol) of di-tert-butylidicarbonate in 150 mL of methylene chloride over about 30 min. The mixture was warmed to room temperature and then stirred for about 17 h. The mixture was
- 10 concentrated and the residue was diluted with chloroform and washed three times each with 10% aqueous HCl, saturated aqueous sodium bicarbonate solution and brine, dried over MgSO₄ and concentrated to give 9.18 g of a clear yellow oil.

B. 3-(R,S)-Benzyl-4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

- 15 To a solution of 5.00 g (19.4 mmol) **3A** in 10 mL of DMF was added 745 mg (7.4 mmol) of sodium hydride (60% oil dispersion) and the mixture was stirred at room temperature for about 15 min. A solution of 3.32 g (19.4 mmol) benzylbromide in 15 mL of DMF was added to the stirring solution by cannula and the mixture was stirred for about 42 h at room temperature. The mixture was diluted with ethyl acetate and
- 20 washed once with water and four times with brine, dried over MgSO₄, and concentrated to give 6.0 g of **3B** as a yellow oil. MS (Cl, NH₃) 348 (MH⁺).

C. 3a-(R,S)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]-pyridine-5-carboxylic acid tert-butyl ester

- A mixture of 4.00 g (11.5 mmol) of **3B** and 530 mg (11.5 mmol) of methylhydrazine
- 25 in 100 mL of ethanol was heated at reflux for about 8 h. The mixture was concentrated and the residue was dissolved in 100 mL toluene and heated at reflux for about 17 h. The mixture was concentrated and the residue was purified by silica gel chromatography using an elution gradient of (15:85 v/v ethyl acetate:hexane) to (75:25 v/v ethyl acetate:hexane) to give 2.6 g of **3C** as a clear colorless oil. MS (Cl, NH₃) 344 (MH⁺).
- 30

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D. 3a-(R,S)-Benzyl-2-methyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one

To 2.60 g (7.6 mmol) of **3C** was added 20 mL of trifluoroacetic acid at about 0 °C and the mixture was stirred for about 2.5 h. Ethyl acetate was added and the solution was washed with 6N NaOH, dried over MgSO₄ and concentrated to give 1.8 g of **3D**. MS (CI, NH₃) 244 (MH⁺).

E. {1-[2-(3a-(R,S)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-(1H-indol-3-ylmethyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 125 mg (4.6 mmol) of **3C** and 1.75 g (0.51 mmol) of **2C** were coupled and the residue was purified by silica gel chromatography using an elution gradient of (6:4 v/v ethyl acetate:hexane) to 7% methanol in ethyl acetate to give 150 mg of **3E**.

F. 2-Amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1R-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

To 150 mg (0.24 mmol) of **3E** in 15 mL of ethanol was added 5 mL of concentrated HCl and the mixture was stirred at room temperature for about 3 h. The mixture was concentrated and the residue was crystallized from ethanol/hexane to give 100 mg of **3F**. MS (CI, NH₃) 515 (MH⁺). ¹HNMR (CD₃OD): δ 7.20 - 6.91 (m, 9 H), 6.56 (m, 1), 5.17 (m, 1 H), 4.05 (m, 1 H), 2.96 (s, 3 H), 2.62 (m, 1 H), 2.38 (m, 1 H), 2.06 (m, 2 H), 1.61 (m, 8 H).

Example 4

2-Amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride and 2-Amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

A. {1-[2-(3a-(R,S)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 1.12 g (4.6 mmol) of **3C** and 1.75 g (0.51 mmol) of **1E** were coupled to give a mixture of diastereomers. The

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residue was purified by silica gel chromatography using an elution gradient of (1:1 v/v ethyl acetate:hexane) to 100% ethyl acetate to give 350 mg of less polar **4A isomer 1** and 250 mg of more polar **4A isomer 2**. MS (CI, NH₃) 606 (MH⁺) for both isomers.

5 **B. 2-Amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2.3.3a.4.6.7-hexahydro-pyrazolo[4.3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride**

To 250 mg (0.41 mmol) of **4A isomer 1** in 15 mL of ethanol was added 5 mL of concentrated HCl and the mixture was stirred at room temperature for about 5 h.
10 The mixture was concentrated and the residue was precipitated from ethanol/hexane and dried under vacuum to give 130 mg of **4B isomer 1**. MS (CI, NH₃) 506 (MH⁺).
¹HNMR (CD₃OD): δ 7.33 (m, 5 H), 7.14 (m, 5 H), 5.22 (m, 1 H), 4.57 (m, 3 H), 3.80 (m, 2 H) 3.14 (m, 1 H), 3.04 (s, 3 H), 2.96 (m, 2 H), 2.61 (m, 2 H), 1.63 (m, 7 H).

C. 2-Amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2.3.3a.4.6.7-hexahydro-pyrazolo[4.3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride
15

To 250 mg (0.41 mmol) of **4A isomer 2** in 15 mL of ethanol was added 5 mL of concentrated HCl and the mixture was stirred at room temperature for about 5 h. The mixture was concentrated and the residue was precipitated from ethanol/hexane
20 and dried under vacuum to give 120 mg of **4C isomer 2**. MS (CI, NH₃) 506 (MH⁺).
¹HNMR (CD₃OD): δ 7.31 (m, 5 H), 7.13 (m, 5 H), 6.78 (m, 1 H), 5.28 (m, 1 H), 4.62 (m, 3 H), 3.81 (M, 2 H), 3.14 (m, 1 H), 2.62 (m, 3 H), 1.58 (m, 7 H).

D. 2-Amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2.3.3a.4.6.7-hexahydro-pyrazolo[4.3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide methanesulfonate
25

Saturated aqueous sodium bicarbonate was added to 3.60 g (6.6 mmol) of **4B isomer 1** and the mixture was extracted with ethyl acetate. The organic layer was dried over MgSO₄ and concentrated. The residue was dissolved in ethyl acetate, cooled to about 0 °C and 0.43 mL (6.6 mmol) of methane-sulfonic acid was added
30 and the mixture was stirred for about 0.5 h. Hexane (200 mL) was added to the solution and the mixture was stirred for about 1h and filtered to give 3.40 g of a white

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solid. The solid was recrystallized from 3% aqueous ethyl acetate to give 2.55 g of **4D isomer 1** as a white crystalline solid. MS (CI, NH₃) 506 (MH⁺).

Example 5

2-Amino-N-[1-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide hydrochloride and
2-Amino-N-[1-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide hydrochloride

A. 2-Oxo-5,6-diphenyl-3-(3-phenyl-allyl)-morpholine-4-carboxylic acid t-butyl ester

10 To an about -78°C solution of 13.8 g (70.0 mmol) of cinnamyl bromide and 4.94 g (14.0 mmol) of t-butyl-(2S,3R)-(+)-6-oxo-2,3-diphenyl-4-morpholine carboxylate in 350 mL of anhydrous THF was added 28 mL (28 mmol) of 1M sodium bistrimethylsilylamide in THF. The mixture was stirred at about -78°C for about 1.5 h and then poured into 750 mL of ethyl acetate. The mixture was washed twice with
15 brine, dried over MgSO₄ and concentrated to give a yellow oil. The oil was stirred in 150 mL of hexane overnight and the precipitated solid was then collected by filtration to give 3.2 g of **5A** as a white solid.

B. 5(S),6(R)-Diphenyl-3(R)-(3-phenyl-allyl)-morpholin-2-one

To 2.97 g (6.33 mmol) of **5A** was added 20 mL of trifluoroacetic acid at about 0°C
20 and the mixture was stirred for about 2 h and then concentrated. The residue was dissolved in water and basified with aqueous NaOH until a pH of 10 was maintained. The mixture was extracted three times with ethyl acetate and the combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give an orange oil which was purified by silica gel chromatography (10:90 v/v ethyl
25 acetate:hexane) to give 880 mg of **5B** as a white solid.

C. 2-(R)-Amino-5-phenyl-pentanoic acid

A mixture of 440 mg (1.19 mmol) of **5B** and 120 mg of palladium chloride in 20 mL of ethanol and 10 mL of THF was hydrogenated at 45 psi. for about 16 h. The mixture was filtered through diatomaceous earth and concentrated, and the residue was
30 triturated with ether to give 240 mg of **5C** as a white solid.

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D. 2-tert-Butoxycarbonylamino-2-methyl-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester

To a slurry of 5.0 g (24.6 mmol) of N-t-BOC- α -methylalanine in 13.5 mL of methylene chloride was added 3.40 g (29.6 mmol) of N-hydroxysuccinimide and 5.65 g (29.6 mmol) of EDC. The slurry was stirred for about 17 h at room temperature. The mixture was diluted with ethyl acetate and washed twice each with water, saturated sodium bicarbonate solution and brine. Dried over MgSO₄ and concentrated. The product was purified by silica gel chromatography (1:1 v/v ethyl acetate:hexanes) to give 5.2 g of the title compound of this part D as a white solid.

10 E. (R)-2-(2-tert-Butoxycarbonylamino-2-methyl-propionylamino)-5-phenyl-pentanoic acid

A mixture of 203 mg (1.05 mmol) of 5D, 378 mg (1.26 mmol) of 5C and 434 mg (3.36 mmol) of diisopropylethylamine in 2 mL of DMF was stirred over-night. The mixture was diluted with ethyl acetate and extracted twice with 1N HCl. The aqueous phase was extracted once with ethyl acetate. The pooled organic extracts were washed three times with water and once with brine. The mixture was dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography using 80% chloroform in hexane followed by 100% chloroform followed by 10% methanol in chloroform to give 127 mg of 5E.

20 F. {1-[1-(3a-(R,S)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butylcarbamoyl]-1-methyl-ethyl)-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 130 mg (0.53 mmol) of 3C and 200 mg (0.53 mmol) of 5E were coupled to give a mixture of diastereomers. The residue was purified by silica gel chromatography using an elution gradient of (1:1 v/v ethyl acetate:hexane) to 100% ethyl acetate to give 40 mg of less polar 5F isomer 1 and 40 mg of more polar 5F isomer 2. MS (CI, NH₃) 604 (MH⁺) for both isomers.

30 G. 2-Amino-N-[1-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide hydrochloride

To 40 mg (0.07 mmol) of 5F isomer 1 in 10 mL of ethanol was added 4 mL of concentrated HCl and the mixture was stirred at room temperature for about 4 h.

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The mixture was concentrated and the residue was precipitated from methylene chloride/hexane and dried under vacuum to give 30 mg of **5G isomer 1**. MS (CI, NH₃) 504 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.19 (m, 10 H), 4.37 (m, 1 H), 3.02 (m, 6 H), 2.67 (m, 4 H), 1.83 (m, 4 H), 1.62 (s, 6 H), 1.28 (m, 1 H).

- 5 H. 2-Amino-N-[1-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide hydrochloride
To 40 mg (0.07 mmol) of **5F isomer 2** in 10 mL of ethanol was added 4 mL of concentrated HCl and the mixture was stirred at room temperature for about 4 h. The mixture was concentrated and the residue was precipitated from methylene
10 chloride/hexane and dried under vacuum to give 30 mg of **5H isomer 2**. MS (CI, NH₃) 504 (MH⁺). ¹HNMR (CD₃OD): (partial) 7.25 (m, 9 H), 6.88 (m, 1 H), 3.04 (s, 3 H), 2.71 (m, 4 H), 2.48 (m, 2 H), 1.75 (m, 4 H), 1.62 (m, 6 H), 1.28 (m, 1 H).

Example 6

- 2-Amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-
15 c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride
A. {1-[2-(3a-(R,S)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-
c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]carbamoyl]-1-methyl-ethyl}-
carbamic acid tert-butyl ester

- According to the method outlined in General Procedure A, 200 mg (0.82 mmol) of **3C**
20 and 320 mg (0.82 mmol) of **1E** were coupled to give a mixture of diastereomers. The residue was purified by silica gel chromatography using an elution gradient of (1:1 v/v ethyl acetate:hexane) to 10% methanol in ethyl acetate to give 170 mg of **6A**.

- B. 2-Amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-
25 pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide
hydrochloride

- To 170 mg (0.28 mmol) of **6A** in 20 mL of ethanol was added 5 mL of concentrated HCl and the mixture was stirred at room temperature for about 2.5 h. The mixture was concentrated and the residue was precipitated from ethanol/hexane to give 70
30 mg of **6B**. MS (CI, NH₃) 506 (MH⁺). ¹HNMR (CD₃OD): δ 7.32 (m, 5 H); 7.16 (m, 5 H), 5.22 (m, 1 H), 4.67 (m, 1 H), 4.55 (m, 2 H), 3.79 m, 2 H), 3.12 (m, 2 H), 3.00 (m, 6 H), 2.71 (m, 3 H), 1.56 (m, 8 H).

Example 7

2-Amino-N-[2-(3a-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

A. 3a-(R,S)-Benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-

5 c]pyridine-5-carboxylic acid tert-butyl ester

To 555 mg (1.60 mmol) of **3B** in 27 mL of ethanol was added 240 mg (1.60 mmol) of ethylhydrazineoxalate and the mixture was heated at reflux for about 4 h. The mixture was concentrated and the residue was purified by silica gel chromatography using an elution gradient of (10:1 v/v hexane:ethyl acetate) to (3:7 v/v hexane:ethyl acetate) to give 357 mg of **7A**. MS (Cl, NH₃) 358 (MH⁺).

B. 3a-(R,S)-Benzyl-2-ethyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one

To 350 mg (0.98 mmol) of **7A** in 3 mL of ethanol was added 1.5 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h. The mixture was concentrated to give 257 mg of **7B**. MS (Cl, NH₃) 258 (MH⁺).

15 C. {1-[2-(3a-(R,S)-Benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 82 mg (0.28 mmol) of **7B** and 100 mg (0.26 mmol) of **2C** were coupled and the residue was purified by silica gel chromatography using an elution gradient of 100% methylene chloride to 2% methanol in methylene chloride to give 110 mg of **7C**. MS (Cl, NH₃) 629 (MH⁺).

D. 2-Amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

25 To 100 mg (0.15 mmol) of **7C** in 2 mL of ethanol was added 1 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h. The mixture was concentrated to give 72 mg of **7D** as a colorless foam. MS (Cl, NH₃) 529 (MH⁺).

Example 8

- 2-Amino-N-[2-(3a-(R)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride and
- 2-Amino-N-[2-(3a-(S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride
- 5 A. {1-[2-(3a-Benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl]-1-methyl-ethyl)-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 85 mg (0.29 mmol) of **7B** and 100 mg (0.26 mmol) of **1E** were coupled to give a mixture of diastereomers. The residue was purified by silica gel chromatography using an elution gradient of 100% methylene chloride to 2% methanol in methylene chloride to give 6 mg of less polar **8A isomer 1** and 11 mg of more polar **8A isomer 2**. MS (CI, NH₃) 620 (MH⁺) for both isomers.

- 15 B. 2-Amino-N-[2-(3a-(R)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

To 5.7 mg (0.009 mmol) of **8A isomer 1** in 1 mL of ethanol was added 0.4 mL of concentrated HCl and the mixture was stirred at room temperature for about 3 h. The mixture was concentrated to give 4.7 mg of **8B isomer 1**. MS (CI, NH₃) 520 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.41 - 7.05 (m, 10 H), 5.20 (m, 1 H), 4.61 (m, 1H), 4.52 (s, 2 H), 3.71 (m, 1 H), 3.60 (m, 1 H), 2.61 (m, 3 H), 1.39 (m, 9 H).

- C. 2-Amino-N-[2-(3a-(S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride
- 25

To 10 mg (0.016 mmol) of **8A isomer 2** in 1 mL of ethanol was added 0.4 mL of concentrated HCl and the mixture was stirred at room temperature for about 3 h. The mixture was concentrated to give 8 mg of **8C isomer 2**. MS (CI, NH₃) 520 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.43 - 7.00 (m, 10 H), 6.81 (m, 1 H), 5.32 (m, 1 H), 4.63 (m, 2 H), 4.53 (m, 1 H), 3.72 (m, 1 H), 1.37 (m, 9 H).

30

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Example 9

2-Amino-N-[2-(2-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

5 A. 2-Benzyl-3-hydroxy-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 800 mg (3.11 mmol) of 3B and 495 mg (3.11 mmol) of benzylhydrazine dihydrochloride and 423 mg (3.11 mmol) of sodium acetate trihydrate in 15 mL of ethanol was heated at reflux for about 17 h. The mixture was concentrated and the residue was dissolved in 100 mL of toluene and heated at reflux for about 48 h. The mixture was diluted with ethyl acetate and washed with brine, dried over MgSO₄ and concentrated and the residue was purified by silica gel chromatography using 100% ethyl acetate followed by 5% methanol in methylene chloride to give 530 mg of 9A as a light brown solid. MS (CI, NH₃) 330 (MH⁺).

15 B. 2-Benzyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridin-3-ol

To 411 mg (1.24 mmol) of 3E in 30 mL of ethanol was added 10 mL of concentrated HCl and the mixture was stirred at room temperature for about 30 min. The mixture was concentrated and the residue was crystallized from methanol/ethyl acetate to give 353 mg of 9B. MS (CI, NH₃) 230 (MH⁺).

20 C. {1-[2-(2-Benzyl-3-hydroxy-2,4,6,7-tetrahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]carbonyl}-1-methyl-ethyl)-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 100 mg (0.38 mmol) of 9B and 145 mg (0.38 mmol) of 1E were coupled and the residue was purified by silica gel chromatography (95:5 v/v methanol:methylene chloride) to give 42 mg of 9C as a white solid. MS (CI, NH₃) 592 (MH⁺).

25 D. 2-Amino-N-[2-(2-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

To 42 mg (0.07 mmol) of 9D in 20 mL of ethanol was added 6 mL of concentrated HCl and the mixture was stirred at room temperature for about 30 min. The mixture was diluted with ethanol concentrated and the residue was precipitated from methanol/ethyl acetate to give 35 mg of 9D as a white solid. MS (CI, NH₃) 492

(MH⁺). ¹HNMR (CD₃OD): (partial) 7.41 - 7.16 (m, 10 H), 5.19 (m, 3 H), 4.48 (m, 4 H), 3.88 (m, 1 H), 3.74 (m, 2 H), 2.68 (m, 2 H), 1.58 (m, 6 H).

Exempl 10

5 2-Amino-N-(2-[3a-(R)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide hydrochloride and

2-Amino-N-(2-[3a-(S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl)-isobutyramide hydrochloride

10 A. 3a-(R,S)-Benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 840 mg (2.42 mmol) of **3B** and 276 mg (2.42 mmol) of 2,2,2-trifluoroethylhydrazine (70% in water) in 20 mL of ethanol was heated at reflux for about 5 h and then concentrated. The residue was dissolved in 40 mL of toluene
15 and heated at reflux for about 17 h. The mixture was concentrated and the residue was purified by silica gel chromatography (9:1 v/v hexane:ethyl acetate) to give 703 mg of **10A** as a yellow oil. MS (CI, NH₃) 412 (MH⁺).

B. 3a-(R,S)-Benzyl-2-(2,2,2-trifluoro-ethyl)-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one

20 To 600 mg (1.46 mmol) of **10A** at about 0 °C was added 3 mL of cold trifluoroacetic acid and the mixture was stirred for about 3 h, allowing the solution to reach room temperature as it did so. The mixture was concentrated and the residue was dissolved in water and the solution was basified to pH 11 with 5N NaOH and then saturated with potassium carbonate. The solution was extracted three times with
25 ethyl acetate and the combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 345 mg of **10B** as an opaque oil. MS (CI, NH₃) 312 (MH⁺).

C. (1-(2-[3a-(R,S)-Benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl)carbamoyl)-1-methyl-ethyl)-carbamic acid tert-butyl ester
30

According to the method outlined in General Procedure A, 137 mg (0.44 mmol) of **10B** and 167 mg (0.44 mmol) of **1E** were coupled to give a mixture of diastereomers.

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The residue was purified by silica gel chromatography using an elution gradient 100% methylene chloride to 5% methanol in methylene chloride to give 128 mg of less polar **10C isomer 1** and 63 mg of more polar **10C isomer 2**. MS (CI, NH₃) 674 (MH⁺) for both isomers

- 5 D. 2-Amino-N-[2-(3a-(R)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

To 120 mg (0.18 mmol) of **10C isomer 1** in 3.5 mL of ethanol was added 1.5 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h.

- 10 The mixture was concentrated to give 94 mg of **10D isomer 1** as an off-white powder. MS (CI, NH₃) 574 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.31 (m, 5 H), 7.18 (m, 5 H), 5.21 (m, 1 H), 4.57 (m, 3 H), 4.26 (m, 1 H), 4.08 (m, 1 H), 3.79 (m, 2 H), 3.09 (m, 4 H), 2.65 (m, 2 H), 1.63 (m, 6 H).

- E. 2-Amino-N-[2-(3a-(S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride
- 15

To 53 mg (0.079 mmol) of **10C isomer 2** in 3.5 mL of ethanol was added 1.5 mL of concentrated HCl and the mixture was stirred at room temperature for about 2 h. The mixture was concentrated to give 41 mg of **10E isomer 2** as a light yellow solid.

- 20 MS (CI, NH₃) 574 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.33 (m, 5 H), 7.15 (m, 4 H), 6.81 (m, 1 H), 5.30 (m, 1 H), 4.67 (m, 4 H), 4.15 (m, 2 H), 3.77 (m, 2 H), 3.09 (m, 3 H), 2.64 (m, 3 H), 1.58 (m, 6 H).

Example 11

- 2-Amino-N-[2-(3a-(R)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide methanesulfonate
- 25 and

2-Amino-N-[2-(3a-(S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide methanesulfonate

- A. 3a-(R,S)-Benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester
- 30

To 2.07 g (5.95 mmol) of **14B** in 40 mL of ethanol was added 0.97 g (7.7 mmol) of tert-butylhydrazine hydrochloride and 0.63 g (7.7 mmol) of sodium acetate and the

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mixture was heated at about 70 °C for about 17 h. The mixture was cooled and the solution decanted from the precipitate and concentrated. The residue was dissolved in 80 mL of toluene and heated at reflux for about 6 h. The mixture was concentrated and the residue was purified by silica gel chromatography (9:1 v/v

5 hexane:ethyl acetate) to give 1.7 g of **11A**. MS (CI, NH₃) 386 (MH⁺).

B. 3a-(R,S)-Benzyl-2-tert-butyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one

To 535 mg (1.39 mmol) of **11A** in 20 mL of methylene chloride was added 225 µL of methanesulfonic acid and the mixture was stirred for about 1.5 h at room
10 temperature. The mixture was diluted with ethyl acetate and washed twice with 1N NaOH and once with brine, dried over Na₂SO₄ and concentrated to give 246 mg of **11B**. MS (CI, NH₃) 286 (MH⁺).

C. {1-[2-(3a-(R,S)-Benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester
15

According to the method outlined in General Procedure A, 246 mg (0.86 mmol) of **11B** and 328 mg of **14F** were coupled to give a mixture of diastereomers. The residue was purified by silica gel chromatography (6:4 v/v hexane/ethyl acetate) to give 250 mg of less polar **11C isomer 1** and 90 mg more polar **11C isomer 2**. MS
20 (CI, NH₃) 648 (MH⁺) for both isomers.

D. 2-Amino-N-[2-(3a-(R)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide methanesulfonate

To 210 mg (0.32 mmol) of **11C isomer 1** in 15 mL of methylene chloride at about 0
25 °C was added 28 µL (0.44 mmol) of methanesulfonic acid. The ice bath was removed and the mixture was stirred for about 3 h, diluted with 15 mL of diethyl ether and the precipitated solid was collected by filtration to give 100 mg of **11D isomer 1**. MS (CI, NH₃) 548 (MH⁺). ¹H NMR (CD₃OD): (partial) δ 7.33 (m, 5 H), 7.27 - 7.07 (m, 5 H), 5.21 (m, 1 H), 4.54 (m, 3 H), 3.86 (m, 3 H), 3.10 (m, 4 H), 2.61 (s, 3 H),
30 1.62 (m, 6 H), 1.18 (s, 9 H).

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E. 2-Amino-N-[2-(3a-(S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide methanesulfonate

To 85 mg (0.13 mmol) of **11C isomer 2** in 10 mL of methylene chloride at about 0 °C was added 21 µL (0.32 mmol) of methanesulfonic acid. The ice bath was removed and the mixture was stirred for about 3 h, diluted with 20 mL of diethyl ether and the precipitated solid was collected by filtration to give 46 mg of **11E isomer 2**. MS (CI, NH₃) 548 (MH⁺). ¹H NMR (CD₃OD): (partial) δ 8.28 (br d, 1 H), 7.32 (m, 5 H), 7.18 (m, 4 H), 6.84 (m, 1 H), 5.31 (m, 1 H), 4.60 (m, 3 H), 3.70 (m, 3 H), 3.18 - 2.92 (m, 3 H), 2.68 (s, 3 H), 1.57 (m, 6 H), 1.13 (s, 9 H).

Example 12

2-Amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide dihydrochloride

A. 4-Oxo-3-(R,S)-pyridin-2-ylmethyl-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

To a solution of 2.00 g (7.8 mmol) of **3A** in 32 mL of THF was added 468 mg (11.7 mmol) of sodium hydride (60% oil dispersion) at about 0 °C and the mixture was stirred for about 30 min. A solution of 762 mg (6.0 mmol) 2-picolyl chloride in 5 mL of THF was added to the stirring solution over about 5 min, followed by the addition of 432 mg (2.6 mmol) of potassium iodide. The ice bath was removed and the mixture was heated for about 17 h at reflux. The mixture was diluted with ethyl acetate and washed once with water and once with brine, dried over MgSO₄, and concentrated. The residue was purified by silica gel chromatography using (6:4 v/v ether:hexane) followed by (6:4 v/v ethyl acetate:hexane) to give 1.2 g of **12A**. MS (CI, NH₃) 349 (MH⁺).

B. 2-Methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 1.20 g (3.45 mmol) of **12A** and 159 mg (3.45 mmol) of methylhydrazine in 20 mL of ethanol was heated at reflux for about 6.5 h. The mixture was concentrated and the residue was dissolved in 25 mL toluene and heated at reflux for about 17 h. The mixture was concentrated and the residue was purified by silica

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gel chromatography (65:35 v/v ethyl acetate:hexane) to give 450 mg of **12B**. MS (CI, NH₃) 345 (MH⁺).

C. 2-Methyl-3a-(R,S)-pyridin-2-ylmethyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one dihydrochloride

5 A mixture of 450 mg (1.30 mmol) of **12B** in 2 mL of 4M HCl/dioxane was stirred at room temperature for about 4.5 h. The mixture was concentrated to give 450 mg of **12C**. MS (CI, NH₃) 245 (MH⁺).

D. {1-[1-(1-(R)-H-Indol-3-ylmethyl)-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

10 According to General Procedure A, 108 mg (0.31 mmol) of **12C** and 122 mg (0.31 mmol) of **2C** were coupled and the residue was purified by silica gel chromatography (95:5 v/v ethyl acetate:methanol) to give 118 mg of **12D**. MS (CI, NH₃) 616 (MH⁺).

E. 2-Amino-N-[1-(R)-(1H-indol-3-ylmethyl)-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide dihydrochloride

A mixture of 110 mg (0.18 mmol) of **12D** in 1 mL of 4M HCl/dioxane was stirred at room temperature for 17 h. The mixture was concentrated to give 51 mg of **12E**. MS (CI, NH₃) 516 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 8.91 - 8.52 (m, 2 H), 8.04 (m, 2 H), 7.76 - 7.50 (m, 3 H), 6.82 (m, 1 H), 4.62 (m, 1 H), 3.36 (s, 3 H), 1.63 (s, 6 H).

Example 13

2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide dihydrochloride

25 A. {1-[1-(R)-Benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

According to General Procedure A, 86 mg (0.27 mmol) of **12C** and 103 mg (0.27 mmol) of **1E** were coupled and the residue was purified by silica gel chromatography (95:5 v/v ethyl acetate:hexane) to give 82 mg of **13A**.

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B. 2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide dihydrochloride

A mixture of 75 mg (0.12 mmol) of 13A in 1 mL of 4M HCl/dioxane was stirred at room temperature for about 17 h. The mixture was concentrated to give 80 mg of 13B. MS (CI, NH₃) 507 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 8.78 (m, 1 H), 8.46 (m, 1 H), 8.13 - 7.82 (m, 2 H), 7.32 (m, 5 H), 4.57 (m, 3 H), 3.96 (m, 1 H), 3.82 (m, 2 H), 1.63 (m, 6 H).

Example 14

10 2-Amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide

A. 4-Oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

To a mixture of 100.0 g (516.4 mmol) of 4-oxo-piperidine-3-carboxylic acid methyl ester and 63 g (516.4 mmol) of 4,4-dimethylaminopyridine in 1 L of methylene chloride at about 0 °C was added a solution of 113.0 g (516.4 mmol) of di-tert-butylidicarbonate in 100 mL of methylene chloride over about 90 min. The mixture was slowly warmed to room temperature and then stirred for about 19 h. The mixture was washed three times each with 10% aqueous HCl, saturated aqueous sodium bicarbonate solution and brine, dried over MgSO₄ and concentrated to give 130.5 g of 14A as an amorphous solid. ¹HNMR (CDCl₃): δ 4.03 (br, 2H); 3.74 (s, 3H), 3.56 (t, 2H), 2.36 (t, 2H), 1.42 (s, 9H).

B. 3-(R)-Benzyl-4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-methyl ester

To a stirred suspension of 11.7 g (293 mmol) of sodium hydride (60% oil dispersion washed twice with 100 mL of hexane) in 100 mL of DMF was added a solution of 65.4 g (254 mmol) of 14A in 150 mL of DMF at about 0 °C over about 45 min. The ice bath was removed and the mixture was stirred at room temperature for about 45 min. The mixture was recooled to about 0 °C and 35.2 mL (296 mmol) of benzylbromide in 200 mL of DMF was added dropwise to the stirring solution and the mixture was stirred for about 23 h at room temperature. To the solution was carefully added 550 mL of water and the mixture was stirred for about 30 min. The mixture was extracted three times with ethyl acetate and the combined organic

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extracts were washed five times with water, once with brine, dried over MgSO_4 and concentrated to give 98 g of a yellow oil. The oil was crystallized from hexane to give 71 g of **14B** as a white solid. MS (CI, NH_3) 348 (MH^+). ^1H NMR (CDCl_3): (partial) δ 7.23 (m, 3 H), 7.13 (m, 2 H), 4.58 (br m, 1 H), 4.18 (br, 1 H), 3.63 (s, 3 H),
5 3.28 - 2.96 (m, 4 H), 2.72 (m, 1 H), 2.43 (m, 1 H), 1.44 (s, 9 H).

C. 3a-(R)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 47.0 g (135 mmol) of **14B**, 38.9 g (270 mmol) of methylhydrazine sulfate and 44.3 g (540 mmol) of sodium acetate in 900 mL of ethanol was heated at reflux
10 for about 17 h under nitrogen. The mixture was concentrated and the residue was dissolved in ethyl acetate and washed three times with water and once with brine, dried over MgSO_4 and concentrated to give a yellow oil. The oil was stirred in 750 mL of hexane for about 3 h to give 41.17 g of **14C** as a white solid. MS (CI, NH_3) 344 (MH^+). ^1H NMR (CDCl_3): (partial) δ 7.19 (m, 3 H), 7.05 (m, 2 H), 4.61 (br m, 2
15 H), 3.24 (m, 1 H), 3.09 (s, 3 H), 3.01 (m, 1 H), 2.62 (m, 4 H), 1.52 (s, 9 H).

D. 3a-(R,S)-Benzyl-2-methyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one hydrochloride

Anhydrous HCl was bubbled through a solution of 24.55 g (71.5 mmol) of **14C** in 800 mL of diethyl ether at about 0 °C for about 12 min. The mixture was stirred for about
20 3 h, during which time a white precipitate formed. The precipitated solid was collected by filtration and to give 19.2 g of **14D**. MS (CI, NH_3) 244 (MH^+). ^1H NMR (CD_3OD): (partial) δ 7.25 (m, 3 H), 7.05 (m, 2 H), 3.77 (m, 2 H), 3.51 (d, 1 H), 3.25 (m, 1 H), 3.17 (m, 3 H), 3.03 (s, 3 H), 2.81 (m, 1 H).

E. 2-tert-Butoxycarbonylamino-2-methyl-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester

To a stirring solution of 100.0 g (492 mmol) of Boc- α -methylalanine and 94.0 g (492 mmol) of EDC in 2 L of methylene chloride at about 0 °C was added 56.63 g (492 mmol) of N-hydroxysuccinimide in portions and the reaction was then allowed to warm to room temperature. The mixture was stirred for about 24 h and washed twice each with saturated aqueous sodium bicarbonate solution and brine, dried over
25
30 Na_2SO_4 and concentrated to give 124.0 g of **14E** as a white solid. ^1H NMR (CDCl_3): δ 4.96 (br, 1H), 2.82 (s, 4H), 1.66 (s, 6H), 1.48 (s, 9H).

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F. 3-(R)-Benzyloxy-2-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionic acid

A mixture of 50.5 g (168 mmol) of **14E**, 33.5 g (168 mmol) of N-t-BOC-O-benzyl-D-serine, and 51.05 g (505 mmol) of triethylamine in 400 mL of dioxane and 100 mL of water was heated at about 45 °C for about 16 h. The mixture was diluted with ethyl acetate and acidified to pH 2 with acetic acid. The layers were separated and the organic phase was washed with brine, dried over Na₂SO₄ and concentrated to give 650 g of **14F** as a white solid. ¹HNMR (CD₃OD): (partial) δ 7.55 (d, 1 H), 7.29 (m, 5 H), 4.52 (m, 1 H), 4.48 (s, 2 H), 3.84 (d of d, 1 H), 3.69 (d of d, 1 H), 1.42 (s, 6 H), 1.38 (s, 9 H).

G. 3a-(R)-Benzyl-2-methyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one L-tartrate

To a mixture of 5.00 g (20.6 mmol) of the free base of **14D** and 3.09 g (20.6 mmol) of L-tartaric acid in 80 mL of acetone and 3.2 mL of water was heated under nitrogen at about 70 °C for about 70 h, during which time the reaction mixture became a thick suspension and an additional 20 mL of acetone was added. The reaction mixture was cooled slowly to room temperature and then filtered. The solid that was collected was washed with acetone and dried under vacuum to give 7.03 g of **14G** as a white solid.

H. 3a-(R)-Benzyl-2-methyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one

To a suspension of 5.00 g (12.7 mmol) of **14G** in 80 mL of methylene chloride at about 0 °C was added 1.72 mL (25.4 mmol) of ammonium hydroxide and the mixture was stirred for about 15 min. The cold solution was filtered and used immediately in the next step.

I. {1-[2-(3a-(R)-Benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

A mixture of 4.83 g (12.7 mmol) of **14F**, the solution from **14G**, 2.60 g (19.1 mmol) of HOAT, and 2.45 g (12.8 mmol) of EDC was stirred at about 0 °C under nitrogen for about 1 h and then warmed to room temperature and stirred for about 16 h. The mixture was filtered and the filtrate was washed with saturated aqueous sodium

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bicarbonate and water, dried over MgSO₄ and concentrated to give 7.35 g of **14I** as a white solid.

J. 2-Amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide

- 5 To 755 mg (1.25 mmol) of **14I** in 7 mL of methylene chloride at about 0 °C was added 3.5 mL of cold trifluoroacetic acid and the mixture was stirred for about 1 h at about 0 °C. The mixture was allowed to warm to room temperature and stirred for about 2 h. The mixture was concentrated and co-evaporated twice with toluene. The residue was dissolved in chloroform and washed twice with saturated aqueous
- 10 sodium bicarbonate and once each with water and brine. The mixture was dried over MgSO₄ and concentrated to give 594 mg of **14J** as an oil.

Example 15

2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide hydrochloride

- 15 A. 2-Methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 3.00 g (11.66 mmol) of **3A** and 537 mg (11.66 mmol) of methylhydrazine in 100 mL of ethanol was heated at reflux for about 17 h. The mixture was concentrated and the residue was dissolved in 100 mL toluene and

20 heated at reflux for about 17 h. The mixture was diluted with ethyl acetate, and washed twice with brine, dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography using an elution gradient of 100% ethyl acetate to 5% methanol in methylene chloride to give 2.28 g of **15A** as a white solid. ¹HNMR (CD₃OD): δ 4.20 (s, 2H), 3.67 (t, 2H), 3.43 (s, 3H), 2.58 (t, 2H), 1.48 (s, 9H).

- 25 B. 2-Methyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one hydrochloride

To 510 mg (2.01 mmol) of **15A** in 30 mL of ethanol was added 10 mL of concentrated HCl and the mixture was stirred at room temperature for about 35 min. The mixture was concentrated and the residue was crystallized from methanol/ethyl acetate to give 425 mg of **15B** as a yellow solid. ¹HNMR (CD₃OD): δ 4.27 (S, 2H),

30 3.71 (S, 3H), 3.56 (T, 2H), 3.05 (T, 2H).

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C. {1-[1-(R)-Benzyloxymethyl-2-(2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl)-carbamic acid tert-butyl ester}

According to the method outlined in General Procedure A, 100 mg (0.53 mmol) of
5 **15B** and 202 mg (0.53 mmol) of **1E** were coupled and the residue was purified by silica gel chromatography (95:5 v/v methylene chloride:methanol) to give 54 mg of **15C** as a white solid. MS (CI, NH₃) 516 (MH⁺).

D. 2-Amino-N-[1-R-benzyloxymethyl-2-(2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide hydrochloride

10 To 54 mg (0.10 mmol) of **15C** in 30 mL of ethanol was added 10 mL of concentrated HCl and the mixture was stirred at room temperature for about 40 min. The mixture was concentrated and the residue was precipitated from methanol/ethyl acetate to give 50 mg of **15D**. MS (CI, NH₃) 416 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.28 (m, 5 H), 5.18 (m, 1 H), 4.69-4.38 (m, 4 H), 3.88 (m, 1 H), 3.73 (m, 2 H), 3.68 (s, 2 H),
15 3.61 (m, 1 H), 2.67 (m, 1 H), 1.57 (s, 6 H).

Example 16

2-Amino-N-[2-(2-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

A. 2-Benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 800 mg (3.11 mmol) of **3A** and 495 mg (3.11 mmol) of benzyl-hydrazine dihydrochloride in 15 mL of ethanol was heated at reflux for about 17 h. The mixture was concentrated and the residue was dissolved in 100 mL toluene and heated at reflux for about 48 h. The mixture was diluted with ethyl acetate, and washed twice
25 with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography using an elution gradient of 100% ethyl acetate to 5% methanol in methylene chloride to give 530 mg of **16A** as a tan solid. MS (CI, NH₃) 330 (MH⁺).

B. 2-Benzyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one hydrochloride

30 To 411 mg (1.24 mmol) of **16A** in 30 mL of ethanol was added 10 mL of concentrated HCl and the mixture was stirred at room temperature for about 30 min. The mixture was concentrated and the residue was crystallized from methanol/ethyl

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acetate to give 353 mg of **16B** as a yellow solid. MS (Cl, NH₃) 230 (MH⁺). ¹HNMR (CD₃OD): δ 7.26-7.40 (m, 5H), 5.22 (s, 2H), 4.12 (s, 2H), 3.53 (t, 2H), 3.00 (t, 2H).

C. (R)-2-(2-tert-Butoxycarbonylamino-2-methyl-propionylamino)-3-(1H-indol-3-yl)-propionic acid

- 5 To a stirring solution of 30.6 g (0.15 mol) of D-tryptophan, 30.4 g (0.30 mol) of N-methylmorpholine in 450 mL of (4:1) dioxane:water, was added 45.0 g (0.15 mol) of **14E** and the mixture was stirred for about 72 h. Excess dioxane was removed by evaporation and water and ethyl acetate were added to the mixture. The pH of the solution was adjusted to 3 with concentrated HCl and the layers were separated.
- 10 The organic layer was washed with water and brine, dried over MgSO₄ and concentrated. The residue was crystallized from ethyl acetate/hexanes to give 37.0 g of an off-white solid.

D. {1-[2-(2-Benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

- 15 According to the method outlined in General Procedure A, 100 mg (0.38 mmol) of **16B** and 202 mg (0.53 mmol) of **16C** were coupled and the residue was purified by silica gel chromatography (95:5 v/v methylene chloride:methanol) to give 45 mg of **16D** as a white solid. MS (Cl, NH₃) 601 (MH⁺).

- 20 E. 2-Amino-N-[2-(2-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide hydrochloride

- To 45 mg (0.07 mmol) of **16D** in 60 mL of ethanol was added 20 mL of concentrated HCl and the mixture was stirred at room temperature for 35 min. The mixture was concentrated and the residue was precipitated from methanol/ethyl acetate to give
- 25 30 mg of **16E**. ¹HNMR (CD₃OD): (partial) δ 7.40 (m, 4 H), 7.25 (m, 3 H), 7.11 (m, 2 H), 6.96 (m, 2 H), 6.81 (m, 1 H), 5.38 - 4.93 (m, 3 H), 4.46 (m, 1 H), 4.22 (m, 1 H), 3.96 (m, 1 H), 3.69 (m, 1 H), 3.18 (m, 1 H), 2.28 (m, 1 H), 1.57 (m, 6 H), 1.38 (m, 1 H).

Example 17

2-Amino-N-[1-benzyloxymethyl-2-(2,3a-dimethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide hydrochlorid

A. 3-Methyl-4-oxo-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-(R,S)-methyl ester

To a solution of 2.00 g (7.77 mmol) **3A** in 30 mL of DMF was added 308 mg (7.77 mmol) of sodium hydride (60% oil dispersion) and the mixture was stirred at room temperature for about 25 min. To the stirring solution was added 0.50 mL (7.77 mmol) of methyl iodide and the mixture was stirred for about 17 h at room temperature. The mixture was diluted with ethyl acetate and washed once with water and four times with brine, dried over MgSO_4 , and concentrated. The residue was purified by silica gel chromatography (7:3 v/v hexane:ethyl acetate) to give 1.75 g of **17A** as a clear oil. MS (CI, NH_3) 272 (MH^+).

B. 2,3a-(R,S)-Dimethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

A mixture of 1.62 g (9.50 mmol) of **17A** and 435 mg (9.50 mmol) of methylhydrazine in 30 mL of ethanol was heated at reflux for about 4 h. The mixture was concentrated and the residue was dissolved in 50 mL toluene and heated at reflux for about 14 h. The mixture was diluted with ethyl acetate, and washed twice with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (7:3 v/v hexane:ethyl acetate) to give 1.00 g of **17B** as a white solid. MS (CI, NH_3) 268 (MH^+).

C. 2,3a-(R,S)-Dimethyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one hydrochloride

To 1.00 g (3.74 mmol) of **17B** in 40 mL of ethanol was added 8 mL of concentrated HCl and the mixture was stirred at room temperature for about 35 min. The mixture was concentrated and the residue was crystallized from methanol/ethyl acetate to give 850 mg of **17C** as a white solid. MS (CI, NH_3) 168 (MH^+).

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D. {1-[1-(R)-Benzyloxymethyl-2-(2,3a-(R,S)-dimethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 150 mg (0.74 mmol) of
5 **17C** and 514 mg (1.35 mmol) of **1E** were coupled and the residue was purified by silica gel chromatography (85:15 v/v hexane:ethyl acetate) to give 185 mg of **17D** as a white solid.

E. 2-Amino-N-[1-(R)-benzyloxymethyl-2-(2,3a-(R,S)-dimethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide hydrochloride
10

To 173 mg (0.33 mmol) of **17B** in 40 mL of ethanol was added 15 mL of concentrated HCl and the mixture was stirred at room temperature for about 1 h. The mixture was concentrated and the residue was diluted with chloroform and washed with saturated aqueous sodium bicarbonate and brine, dried over Na₂SO₄
15 and the residue was purified by silica gel chromatography using an elution gradient of 100% ethyl acetate to 10% diethylamine in ethyl acetate. The residue was dissolved in ethanol and acidified with aqueous HCl. The mixture was concentrated and the residue was crystallized from methanol/ethyl acetate to give 65 mg of **17E** as a white solid. MS (CI, NH₃) 502 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 7.32 (m, 5 H),
20 5.14 (m, 1 H), 4.53 (m, 3 H), 3.71 (m, 3 H), 2.97 (m, 1 H), 2.83 (m, 1 H), 2.57 (m, 1 H), 1.98 (m, 2 H), 1.61 (m, 6 H), 1.38 (s, 3 H).

Example 18

2-Amino-N-[2-(3a-(R)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride and
25 2-Amino-N-[2-(3a-(S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

A. 3-Benzyl-4-oxo-piperidine-3-carboxylic acid methyl ester

To 200 mg (0.58 mmol) of **3B** at about 0 °C was added 5 mL of cold trifluoroacetic acid and the mixture was stirred for about 1 h. The mixture was concentrated and
30 the residue was co-evaporated with ethyl acetate and hexane. To the residue was added 2N NaOH to make it basic and the mixture was extracted with chloroform.

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The combined organic extracts were dried over MgSO_4 and concentrated to give **18A** in quantitative yield.

B. 3-(R,S)-Benzyl-1-[3-benzyloxy-2-(R)-(2-tert-butoxycarbonylamino-2-methyl-propionylamino)-propionyl]-4-oxo-piperidine-3-carboxylic acid methyl ester

- 5 According to the method outlined in General Procedure A, 1.77 g (7.16 mmol) of **18A** and 3.04 g (8.0 mmol) of **14F** were coupled to give a mixture of diastereomers. The residue was purified by silica gel chromatography (7:3 v/v hexane:ethyl acetate) to give 820 mg of less polar **18B isomer 1** and 1.14 g more polar **18B isomer 2**. MS (Cl, NH_3) 611 (MH^+) for both isomers.

- 10 C. {1-[2-(3a-(R,S)-Benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

- To a solution of 820 mg (1.32 mmol) of **18B isomer 1** in 13 mL of ethanol was added 342 mg (2.63 mmol) of hydrazine sulfate and 431 mg (5.26 mmol) of sodium acetate and the mixture was heated at reflux for about 17 h. The mixture was concentrated and the residue was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine, dried over MgSO_4 and concentrated. The residue was purified by silica gel chromatography using an elution gradient of 75% ethyl acetate in hexane to 100% ethyl acetate to give 550 mg of **18C isomer 1**.

- 20 To a solution of 1.14 g (1.86 mmol) of **18B isomer 2** in 20 mL of ethanol was added 485 mg (3.73 mmol) of hydrazine sulfate and 613 mg (7.48 mmol) of sodium acetate and the mixture was heated at reflux for about 17 h. The mixture was concentrated and the residue was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate and brine, dried over MgSO_4 and concentrated. The residue was purified by silica gel chromatography (75:25 v/v ethyl acetate/hexane) to give 710 mg of **18C isomer 2**.

D. 2-Amino-N-[2-(3a-(R)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

- To 200 mg (0.34 mmol) of **18C isomer 1** in 12 mL of ethanol was added 6 mL of concentrated HCl and the mixture was stirred at room temperature for about 2.5 h. The mixture was concentrated and co-evaporated three times with ethanol to give 20 mg of **18D isomer 1**. MS (Cl, NH_3) 492 (MH^+). ^1H NMR (CD_3OD): (partial) δ 8.42

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(br d, 1 H), 7.35 (m, 5 H), 7.18 (m, 5 H), 5.23 (m, 2 H), 4.91 (m, 1 H), 4.54 (m, 4 H), 3.80 (m, 2 H), 3.63 (m, 1 H), 3.12 (m, 1 H), 3.07 (m, 3 H), 2.61 (m, 3 H), 1.62 (m, 6 H), 1.39 (m, 1 H).

E. 2-Amino-N-[2-(3a-(S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide hydrochloride

To 200 mg (0.34 mmol) of **18C isomer 2** in 20 mL of ethanol was added 10 mL of concentrated HCl and the mixture was stirred at room temperature for about 2.5 h. The mixture was concentrated and co-evaporated three times with ethanol to give 30 mg of **18E isomer 2**. MS (CI, NH₃) 492 (MH⁺). ¹HNMR (CD₃OD): (partial) δ 8.29 (br d, 1 H), 7.30 (m, 5 H), 7.11 (m, 4 H), 6.88 (m, 1 H), 5.29 (m, 1 H), 4.92 (m, 1 H), 4.62 (m, 3 H), 3.91-3.70 (m, 3 H), 3.22-2.95 (m, 3 H), 2.66 (m, 3 H), 1.57 (m, 6 H), 1.30 (m, 1 H), 0.89 (m, 1 H).

Example 19

2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-thiazol-4-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide dihydrochloride

A. 4-Oxo-3-(R,S)-thiazol-4-ylmethyl-piperidine-1,3-dicarboxylic acid 1-tert-butyl ester 3-ethyl ester

To a solution of 300 mg (1.10 mmol) of **1A** in 5 mL of THF at about 0 °C was added 67 mg (1.66 mmol) of sodium hydride (60% oil dispersion) and the mixture was stirred for about 30 min. A solution of 204 mg (1.21 mmol) of 4-chloromethyl-thiazole (Hsiao, C. N; Synth. Comm. 20, p. 3507 (1990)) in 5 mL of THF was added to the cold solution, followed by 87 mg (0.53 mmol) of potassium iodide and the mixture was heated at reflux for about 17 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over Na₂SO₄ and concentrated and the residue was purified by silica gel chromatography (7:3 v/v hexane:ethyl acetate) to give 90 mg of the title compound. MS (CI, NH₃) 648 (MH⁺).

B. 2-Methyl-3-oxo-3a-(R,S)-thiazol-4-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carboxylic acid tert-butyl ester

To 90 mg (0.24 mmol) of **19A** in 2 mL of ethanol was added 11.2 mg (0.24 mmol) of methylhydrazine and the mixture was heated at reflux for about 17 h. An additional

33.6 mg (0.72 mmol) of methylhydrazine was added and the mixture was heated at reflux for about 7 h. The mixture was concentrated and the residue was dissolved in 3 mL of toluene and heated at reflux for about 17 h. The mixture was concentrated and the residue was purified by silica gel chromatography (6:4 v/v hexane:ethyl acetate) to give 44 mg of **19B**. MS (CI, NH₃) 648 (MH⁺).

C. 2-Methyl-3a-(R,S)-thiazol-4-ylmethyl-2,3a,4,5,6,7-hexahydro-pyrazolo[4,3-c]pyridin-3-one dihydrochloride

A mixture of 44 mg (0.10 mmol) of **19B** in 1 mL of 4M HCl in dioxane was stirred at room temperature for about 4 h. The mixture was concentrated and co-evaporated with methylene chloride to give 40 mg of **19C**. MS (CI, NH₃) 251 (MH⁺).

D. {1-[1-(R)-Benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-thiazol-4-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethylcarbamoyl]-1-methyl-ethyl}-carbamic acid tert-butyl ester

According to the method outlined in General Procedure A, 40 mg (0.12 mmol) of **19C** and 39 mg (0.12 mmol) of **14F** were coupled and the residue was purified by silica gel chromatography (9:1 v/v ethyl acetate:hexane) to give 40 mg of **19D**. MS (CI, NH₃) 613 (MH⁺).

E. 2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-thiazol-4-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-isobutyramide dihydrochloride

A mixture of 40 mg (0.06 mmol) of **19D** in 1 mL of 4M HCl in dioxane was stirred at room temperature for about 5 h. The mixture was concentrated and co-evaporated with methylene chloride to give 40 mg of **19E**. MS (CI, NH₃) 513 (MH⁺).

Example 20

25 2-Amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide L-tartaric acid salt

To 4.6 g of the title compound of Example 14 in 20 mL of methanol, a solution of 1.36 g of L-tartaric acid in 20 mL of methanol was added at about 0° C. The mixture was warmed to room temperature, stirred for about 40 min and concentrated *in vacuo*. The residue was diluted with 220 mL of ethyl acetate, heated at reflux for

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about 1.5 h, then stirred at about 72° C for about 18 h. The mixture was cooled to room temperature, and filtered to give 5.78 g of the title compound as a colorless crystalline solid.

Example 21

5 3-Benzyl-3-methoxycarbonylmethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

A. 3-Benzyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

A mixture of the β -ketoester (4480 mg, 12.9 mmol) and LiCl (1100 mg, 25.8 mmol) was heated in DMF (2.0 ml) at about 120 °C for about 17 h. The reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 100 mL).

10 The combined extracts were dried and concentrated *in vacuo*. The crude product was chromatographed on SiO₂ using 20% ethyl acetate/hexanes to give 1320 mg of the desired product as a yellow oil. ¹H NMR (250 MHz, CDCl₃): d: 7.4 (m, 5H), 4.2 (m, 1H), 3.4 (m, 1 H), 3.3 (dd, 1 H), 3.05 (dd, 1 H), 2.7 (m, 1H), 2.55 (m, 4H), 1.5 (s, 9H); MS (APCI): 190 (M+1- BOC).

15 B. 3-Benzyl-3-methoxycarbonylmethyl-4-oxo-piperidine-1-carboxylic acid tert-butyl ester

A solution of the product from Step A of Example 21 above (1320 mg, 4.56 mmol), pyrrolidine (972 mg, 13 mmol) and p-toluenesulfonic acid (33 mg) in benzene (30 ml) was refluxed through 3 Å molecular sieves for about 17 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in benzene (10 ml) and cooled to about 0 °C. Methyl bromoacetate (1530 mg, 10 mmol) was added dropwise. The reaction mixture was slowly allowed to warm to room temperature and then was heated under reflux for about 17 h at which point H₂O (5 mL) was added. After refluxing for about another 2

25 h, the reaction mixture was cooled to room temperature and extracted with EtOAc (3 x 100 ml). The combined organic extracts were dried and concentrated *in vacuo*. The crude residue was chromatographed on SiO₂-gel using 15% ethyl acetate/hexanes to give 280 mg of product. ¹H NMR (250 MHz, CDCl₃): d 7.35 (m, 5 H), 4.5 (m, 1 H), 3.8 (s, 3H), 3.4 (dd, 1 H), 3.1 (m, 1 H), 2.85 (m, 4H), 2.6 (m, 1 H), 2.4 (m, 1
30 H), 1.5 (s, 9 H); MS (APCI): 362 (M+1).

Example 22**6-Oxo-1-phenyl-cyclohexane-1,3-dicarboxylic acid 3-tert-butyl ester 1-methyl ester**

A solution of diphenylmercury (890 mg, 2.5 mmol) in CHCl_3 (4 ml) under N_2 was heated to about 40 °C. Lead tetraacetate (1110 mg, 2.5 mmol) was added in small portions and the greenish yellow solution was stirred at about 40 °C for about 0.5 h. The β -ketoester (520 mg, 2.0 mmol) was then added, followed by pyridine (0.2 ml, 2.5 mmol). After about 5 h at about 40 °C, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in ether (100 ml) and filtered. The filtrate was washed with 3N H_2SO_4 (3x), dried and concentrated to give 616 mg of a yellow solid. Flash chromatography over SiO_2 -gel using 25% ethyl acetate/hexanes provided 368 mg of the desired product. ^1H NMR (400 MHz, CDCl_3): d 7.15 (m, 5 H), 4.4 (s, 2 H), 3.7 (s, 5 H), 2.6 (s, 2 H), 1.5 (s, 9H); MS (APCI): 334 (M+1)

Example 23**(D)-2-Amino-3-(2,4-dichloro-benzyloxy)-propionic acid hydrochloride****A. (D)-2-tert-Butoxycarbonylamino-3-(2,4-dichloro-benzyloxy)-propionic acid**

To a stirred solution of Boc-D-serine (8.2 g, 40 mmol) in DMF (75 ml) at about 0°C was added NaH (60% dispersion, 3.2 g, 80 mmol) over about a 10 minute period. The reaction mixture was stirred for about 1.75 h at about 0 °C, then about 0.25 h at room temperature. After cooling to about 0 °C, a solution of 2,4-dichlorotoluene (5.56 ml, 40 mmol) in DMF (5 ml) was added dropwise. The reaction mixture was allowed to warm to about 23 °C and was stirred for about 17 h, then was partitioned between di-isopropylether and 10% HCl. The aqueous solution was extracted with di-isopropyl ether (2x). The combined extracts were washed with saturated aqueous brine, dried and concentrated to give 14.75 g of crude product which was used without further purification. ^1H NMR (400 MHz, CDCl_3): d 7.6-7.2 (m, 3 H), 5.4 (d, 1 H), 4.6 (s, 2 H), 4.0 (d, 1 H), 3.8 (dd, 2 H), 1.1 (s, 9H); MS (APCI): 264,266 (M+1, M+2).

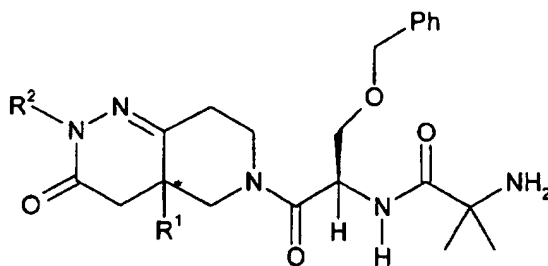
B. (D)-2-Amino-3-(2,4-dichloro-benzyloxy)-propionic acid hydrochloride

The product from step A of Example 23 above (14.7 g, 40 mmol) was stirred in 4 M HCl/dioxane (100 ml) for about 17 h. The reaction mixture was concentrated *in vacuo* to give 12 g of a pale yellow solid (100%). MS (APCI): 265 (M+1).

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Example 24

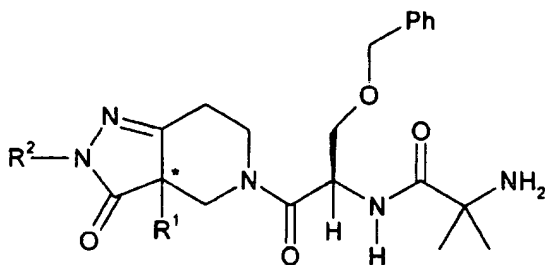
Example 24 having the formula shown below,



- wherein R¹ is -CH₂-phenyl and R² is methyl, was synthesized in an analogous manner to the procedures described in Examples 3C to 3F using the title compound of Example 21 as starting material. Both the R,R and S,R diastereomers (* indicates the other stereoisomer center at the C-3 carbon of the above structure) were isolated. Mass spec. (M+1)= 520; MS method = particle bombardment.

Examples 25 and 26

- Examples 25 and 26 having the formula shown below,

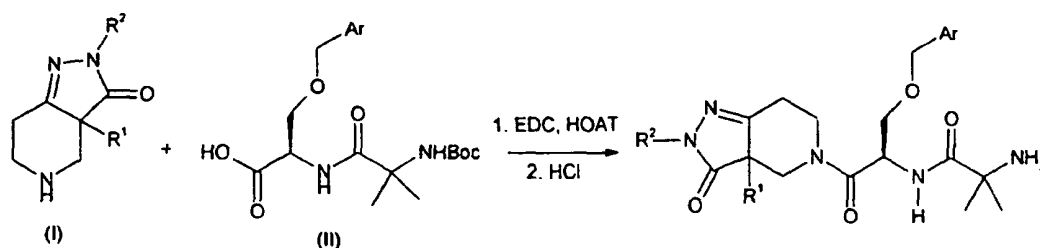


- wherein for both examples 25 and 26 R¹ is phenyl and R² is methyl, where example 25 is the R,R isomer and example 26 is the S,R isomer. Examples 25 and 26 were synthesized in an analogous manner to the procedures described in Examples 3C to 3F using the title compound of Example 22 as starting material followed by chromatographic separation of the two separate isomers. Mass spec. of each example (M+1)= 493, MS method= particle bombardment.

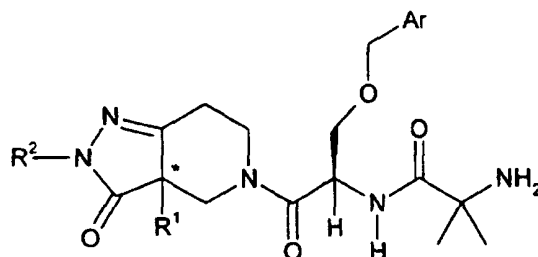
Examples 27- 159

- Examples 27 to 159 listed in the table below, were prepared according to the scheme illustrated below by coupling the appropriately substituted pyrazalone-piperidine of formula I (in the below scheme) with the (D)-OBnSer derivative II (in the below scheme) in an analogous manner to the procedures described in Examples 3E and 3F.

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The pyrazalone-piperidines of formula I were prepared analogously according to the procedures described in Examples 3B and 3C starting with the appropriate alkylating agent and alkyldiazine; the (D)-OBnSer derivatives (II) were prepared in three steps analogously to the procedures described in Example 23A, Example 23B and Example 5F.



10

Ex. #	Isomer	R ²	R ¹ = -CH ₂ -A ¹	Ar	MS	MS Method
27	d1	H	2-pyridyl	phenyl	493	PB
28	d1	H	4-thiazolyl	phenyl	499	PB
29	d2	H	4-thiazolyl	phenyl	499	PB
30	d1	H	5-thiazolyl	phenyl	499	APCI
31	d1	Me	phenyl	2,4-di-Cl-Ph	574.5	APCI
32	d1	Me	phenyl	2,4-di-F-Ph	542	PB
33	d1	Me	phenyl	[2,3-O-CH ₂ -O]Phenyl	550.2	PB
34	d1	Me	phenyl	2-CF ₃ -Ph	575	PB
35	d1	Me	phenyl	2-Me-Ph	520	PB
36	d1	Me	phenyl	2-pyridyl	507	PB
37	d1	Me	phenyl	3,4-di-F-Ph	542	PB
38	d1,2	Me	phenyl	3,5-di-CF ₃ -Ph	642	PB
39	d1	Me	phenyl	3,5-di-Cl-Ph	576	APCI

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40	d2	Me	phenyl	3-CF ₃ -Ph	575	APCI
41	d1	Me	phenyl	3-Cl-Ph	540	APCI
42	d1	Me	phenyl	3-Cl-thiophene	546, 548	APCI
43	d1	Me	phenyl	3-F-4-Cl-Ph	560	APCI
44	d1	Me	phenyl	3-Me-Ph	520	PB
45	d1	Me	phenyl	4-Cl-Ph	540	PB
46	d1	Me	phenyl	4-pyridyl	507	PB
47	d1	Me	phenyl	4-thiazolyl	513	PB
48	d1	Me	phenyl	5-thiazolyl	513	APCI
49	d1,2	Me	phenyl	benzisoaxazolyl	547	PB
50	d1	Me	phenyl	4-pyrimidinyl	508	PB
51	d1,2	Me	4-Ph-Ph	4-thiazolyl	589	APCI
52	d1,2	Me	4-Ph-Ph	2-pyridyl	583	APCI
53	d1	Me	4-F-Ph	phenyl	524	PB
54	d2	Me	4-F-Ph	phenyl	524	PB
55	d1	Me	4-F-Ph	3-Cl-Ph	558	PB
56	d2	Me	4-F-Ph	3-Cl-Ph	558	PB
57	d1	Me	4-F-Ph	3,4-di-F-Ph	560	APCI
58	d2	Me	4-F-Ph	3,4-di-F-Ph	560	APCI
59	d1,2	Me	4-F-Ph	2-pyridyl	525	APCI
60	d1,2	Me	4-F-Ph	2-CF ₃ -Ph	592	APCI
61	d1	Me	4-CF ₃ -Ph	4-Cl-Ph	609	APCI
62	d1,2	Me	4-CF ₃ -Ph	4-Cl-Ph	609	APCI
63	d1,2	Me	3-pyridyl	phenyl	508	PB
64	d1	Me	3-phenyl	3-pyridyl	508	PB
65	d1	Me	2-quinolinyl	phenyl	594	PB
66	d2	Me	2-quinolinyl	phenyl	594	PB
67	d1	Me	2-pyridyl	phenyl	506	PB
68	d2	Me	2-pyridyl	phenyl	506	PB
69	d1,2	Me	2-pyridyl	3-F-4-Cl-Ph	559, 561	APCI
70	d1	Me	2-pyridyl	3-Cl-thiophene	547, 549	APCI
71	d1	Me	2-pyridyl	3-CF ₃ -Ph	575	PB
72	d1,2	Me	2,4-di-F-Ph	3,4-di-F-Ph	579	APCI
73	d1,2	Me	2,4-di-F-Ph	2-pyridyl	544	PB
74	d1	Me	4-thiazolyl	phenyl	513	APCI
75	d2	Me	4-thiazolyl	phenyl	513	PB

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76	d1	Me	5-thiazolyl	phenyl	513	PB
77	d1	Et	2-pyridyl	phenyl	521	PB
78	d1,2	Et	phenyl	4-thiazolyl	541	APCI
79	d1	Et	phenyl	3,5-di-CF ₃ -Ph	656	PB
80	d1,2	Et	phenyl	3,4-di-F-Ph	556	PB
81	d1	Et	2,4-di-F-Ph	2,4-di-F-Ph	593	APCI
82	d2	Et	2,4-di-F-Ph	2,4-di-F-Ph	593	APCI
83	d1	Et	2,4-di-F-Ph	2-CF ₃ -Ph	625	APCI
84	d2	Et	2,4-di-F-Ph	2-CF ₃ -Ph	625	APCI
85	d1	Et	2,4-di-F-Ph	3,4-di-F-Ph	593	APCI
86	d2	Et	2,4-di-F-Ph	3,4-di-F-Ph	593	APCI
87	d1	Et	2-pyridyl	3,4-di-F-Ph	607	PB
88	d2	Et	2-pyridyl	3,4-di-F-Ph	607	PB
89	d1	Et	4-CF ₃ -Ph	2,4-di-F-Ph	625	APCI
90	d2	Et	4-CF ₃ -Ph	2,4-di-F-Ph	625	APCI
91	d1	Et	4-CF ₃ -Ph	3-Cl-Ph	623	APCI
92	d1	Et	4-CF ₃ -Ph	4-Cl-Ph	623	APCI
93	d2	Et	4-CF ₃ -Ph	4-Cl-Ph	623	APCI
94	d1	Et	4-CH ₃ -Ph	3-Cl-Ph	568	APCI
95	d2	Et	4-CH ₃ -Ph	3-Cl-Ph	568	APCI
96	d1	Et	4-Cl-Ph	3,4-di-F-Ph	590	PB
97	d2	Et	4-Cl-Ph	3,4-di-F-Ph	590	PB
98	d1	Et	4-Cl-Ph	3-5-di-Cl-Ph	622	PB
99	d2	Et	4-Cl-Ph	3-5-di-Cl-Ph	622	PB
100	d1	Et	4-Cl-Ph	3-Cl-Ph	589	PB
101	d2	Et	4-Cl-Ph	3-Cl-Ph	589	PB
102	d1	Et	4-F-Ph	3,4-di-F-Ph	574	PB
103	d2	Et	4-F-Ph	3,4-di-F-Ph	574	PB
104	d1	Et	4-F-Ph	3-Cl-Ph	572	APCI
105	d2	Et	4-F-Ph	3-Cl-Ph	572	APCI
106	d1,2	Et	4-Me-Ph	2-CF ₃ -Ph	602	APCI
107	d1,2	Et	4-Me-Ph	3,4-di-F-Ph	570	APCI
108	d1,2	CF ₃ CH ₂	phenyl	4-thiazolyl	595	APCI
109	d1	CF ₃ CH ₂	phenyl	3-CF ₃ -Ph	642.3	APCI
110	d1	CF ₃ CH ₂	phenyl	3,5-di-Cl-Ph	643	APCI
111	d2	CF ₃ CH ₂	phenyl	3,5-di-Cl-Ph	644	APCI

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112	d1	CF ₃ CH ₂	phenyl	3,4-di-F-Ph	610.2	APCI
113	d2	CF ₃ CH ₂	phenyl	3,4-di-F-Ph	610.2	APCI
114	d1	CF ₃ CH ₂	phenyl	3,5-di-Cl-Ph	643	APCI
115	d2	CF ₃ CH ₂	phenyl	3,5-di-Cl-Ph	644	APCI
116	d1	CF ₃ CH ₂	phenyl	3-CF ₃ -Ph	642.3	APCI
117	d1	CF ₃ CH ₂	phenyl	3,4-di-F-Ph	610.2	APCI
118	d2	CF ₃ CH ₂	phenyl	3,4-di-F-Ph	610.2	APCI
119	d1,2	CF ₃ CH ₂	phenyl	4-thiazolyl	595	APCI
120	d1,2	CF ₃ CH ₂	2,4-di-Cl-Ph	2-pyridyl	643	APCI
121	d1,2	CF ₃ CH ₂	2,4-di-Cl-Ph	4-thiazolyl	649	APCI
122	d1	CF ₃ CH ₂	2,4-F-Ph	2-CF ₃ -Ph	679	APCI
123	d2	CF ₃ CH ₂	2,4-F-Ph	2-CF ₃ -Ph	679	APCI
124	d1	CF ₃ CH ₂	2,4-F-Ph	3,4-di-F-Ph	647	APCI
125	d2	CF ₃ CH ₂	2,4-F-Ph	3,4-di-F-Ph	647	APCI
126	d1,2	CF ₃ CH ₂	2,4-F-Ph	4-thiazolyl	617	PB
127	d1	CF ₃ CH ₂	2-pyridyl	2,4-di-Cl-Ph	643	APCI
128	d2	CF ₃ CH ₂	2-pyridyl	2,4-di-Cl-Ph	643	APCI
129	d1	CF ₃ CH ₂	2-pyridyl	2,4-di-F-Ph	611	PB
130	d2	CF ₃ CH ₂	2-pyridyl	2,4-di-F-Ph	611	PB
131	d1	CF ₃ CH ₂	2-pyridyl	2-CF ₃ -4-F-Ph	661	APCI
132	d1	CF ₃ CH ₂	2-pyridyl	2-CF ₃ -Ph	643	PB
133	d2	CF ₃ CH ₂	2-pyridyl	2-CF ₃ -Ph	643	PB
134	d1	CF ₃ CH ₂	2-pyridyl	3,4-di-F-Ph	611	PB
135	d2	CF ₃ CH ₂	2-pyridyl	3,4-di-F-Ph	611	PB
136	d1	CF ₃ CH ₂	2-pyridyl	3,5-di-Cl-Ph	643	APCI
137	d1	CF ₃ CH ₂	2-pyridyl	3-Cl-Ph	609	PB
138	d1	CF ₃ CH ₂	2-pyridyl	3-Cl-thiophene	615, 617	APCI
139	d1,2	CF ₃ CH ₂	2-pyridyl	3-F-4-Cl-Ph	627, 629	APCI
140	d1	CF ₃ CH ₂	2-pyridyl	3-OCF ₃ -Ph	659	APCI
141	d1	CF ₃ CH ₂	2-pyridyl	4-Cl-Ph	609	PB
142	d2	CF ₃ CH ₂	2-pyridyl	4-Cl-Ph	609	PB
143	d1,2	CF ₃ CH ₂	3-pyridyl	2,4-di-F-Ph	612	APCI
144	d1,2	CF ₃ CH ₂	3-pyridyl	2-CF ₃ -Ph	644	APCI
145	d1,2	CF ₃ CH ₂	3-pyridyl	4-Cl-Ph	610	APCI
146	d1	CF ₃ CH ₂	4-CH ₃ -Ph	3-Cl-Ph	622	APCI
147	d2	CF ₃ CH ₂	4-CH ₃ -Ph	3-Cl-Ph	622	APCI

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148	d1	CF ₃ CH ₂	4-Cl-Ph	3,4-di-F-Ph	644	PB
149	d2	CF ₃ CH ₂	4-Cl-Ph	3,4-di-F-Ph	644	PB
150	d1	CF ₃ CH ₂	4-Cl-Ph	3,5-di-Cl-Ph	675	PB
151	d2	CF ₃ CH ₂	4-Cl-Ph	3,5-di-Cl-Ph	675	PB
152	d2	CF ₃ CH ₂	4-Cl-Ph	3-Cl-Ph	642	PB
153	d1	CF ₃ CH ₂	4-Cl-Ph	3-Cl-Ph	642	PB
154	d1	CF ₃ CH ₂	4-F-Ph	3,4-di-F-Ph	628	PB
155	d2	CF ₃ CH ₂	4-F-Ph	3,4-di-F-Ph	628	PB
156	d1	CF ₃ CH ₂	4-F-Ph	3-Cl-Ph	626	PB
157	d2	CF ₃ CH ₂	4-F-Ph	3-Cl-Ph	626	PB
158	d1,2	CF ₃ CH ₂	4-Me-Ph	2-CF ₃ -Ph	656	APCI
159	d1,2	CF ₃ CH ₂	4-Me-Ph	3,4-di-F-Ph	624	APCI

Note: in the above table, the isomer designation refers to the stereochemistry at the C-3 position (indicated by the "*" in the structure) of the pyrazalone-piperidine group; d1 and d2 refer to isomers that were chromatographically separated; d1,2 refers to a mixture of isomers. Abbreviations used in the table above are: Ph is phenyl; PB is particle bombardment; and APCI is atmospheric pressure chemical ionization. The following are NMR data for the compounds of the above table as indicated.

Example 37: ¹H NMR (400 MHz, d4-MeOH): d 7.2 (m, 5H), 5.2 (t, 1H), 4.6 (m, 3H), 3.8 (d, 2H), 3.1 (d, 1H), 3.0 (s, 3H), 2.6 (dd, 2H), 1.6 (s, 6H).

Examples 67 & 68: ¹H NMR (300 MHz, d4-MeOH): d 8.85 (s, 1H), 8.6 (t, 1H), 8.1 (d, 1H), 8.0 (t, 1H), 7.35 (s, 5H), 5.15 (s, 1H), 4.6 (bs, 3H), 3.85 (m, 2H), 3.65 (m, 2H), 3.2 (s, 3H), 2.75 (m, 2H), 1.65 (s, 6H).

Example 128: ¹H NMR (400 MHz, d4-MeOH): d 8.8 (s, 1H), 8.6 (s, 1H), 8.5 (t, 1H), 7.96 (t, 1H), 7.9 (d, 1H), 7.45 (d, 1H), 7.33 (d, 1H), 5.2 (s, 1H), 4.6 (s, 3H), 4.4 (m, 1H), 4.2 (m, 2H), 3.9 (m, 4H), 3.5 (m), 3.2 (m, 2H), 2.8 (dd, 2H), 1.6 (s, 6H).

Examples 129 & 130: ¹H NMR (400 MHz, d4-MeOH): d 8.76 (s, 1H), 8.50 (t, 1H), 7.92 (dt, 2H), 7.43 (q, 1H), 6.90 (t, 1H), 5.20 (m, 1H), 4.90 (m), 4.30 (m, 1H), 4.20 (m, 1H), 3.7 - 3.4 (m), 3.30 (s, 2H), 3.20 (m, 1H), 2.80 (dd, 2H), 1.60 (s, 6H).

Example 137: ¹H NMR (300 MHz, d4-MeOH): d 8.7 (1, 1H), 8.45 (t, 1H), 7.9 (t, 2H), 7.25 (m, 4H), 5.2 (m, 1H), 4.95 (d, 1H), 4.6 (s, 2H), 4.3 (m, 1H), 3.8 (t, 2H), 3.5 (dd, 2H), 2.8 (m, 1H), 2.8 (dd, 2H), 1.6 (s, 6H).

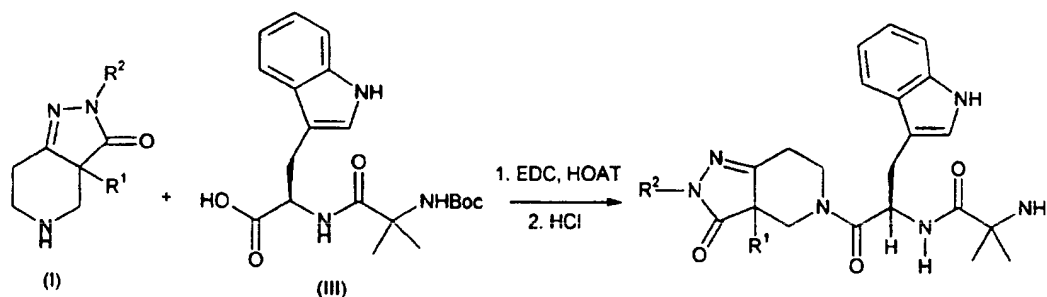
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Example 138: ^1H NMR (400 MHz, $\text{d}_4\text{-MeOH}$): δ 8.8 (dd, 1H), 8.6 (s, 1H), 8.5 (t, 1H), 7.95 (t, 1H), 7.9 (s, 1H), 7.3 (s, 1H), 7.0 (s, 1H), 5.2 (s, 1H), 4.85 (s, 3H), 4.4 (m, 1H), 4.18 (m, 1H), 3.8 (m, 2H), 3.5 (dd, 2H), 3.2 (d, 2H), 2.8 (dd, 2H), 1.6 (s, 6H).

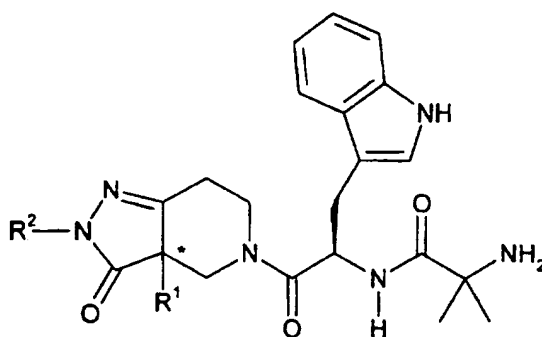
Examples 141 & 142: ^1H NMR (300 MHz, $\text{d}_4\text{-MeOH}$): δ 8.75 (m, 1 H), 8.5 (m, 1 H),
 5 7.9 (m, 2 H), 7.3 (s, 2 H), 5.2 (m, 1 H), 4.65 (m, 1 H), 4.55 (s, 2 H), 4.35 (m, 1 H),
 4.20 (m, 1 H), 3.8 (t, 1 H), 3.5 (dd, 2 H), 3.15 (d, 1 H), 2.8 (dd, 2 H), 1.6 (s, 2 H).

Examples 160- 179

Examples 160 to 179 shown in the table below were prepared according to the scheme illustrated below by coupling the appropriately substituted pyrazalone-piperidine (I) (in the scheme) with the (D)-Trp derivative (III) (see Example 2C) in an
 10 analogous manner to the procedures described in Examples 3E and 3F.



15



Ex. #	Isomer	R ²	R ¹ = -CH ₂ -A ¹	MS	MS Method
160	d1	Me	4-CF ₃ -Ph	584	APCI
161	d1,2	Me	4-CF ₃ -Ph	584	APCI
162	d1	Me	4-F-Ph	533	PB
163	d2	Me	4-F-Ph	533	PB

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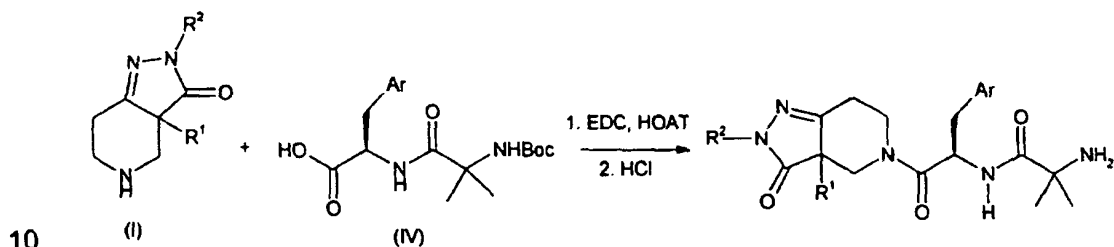
164	d1	Me	4-Ph-Ph	591	APCI
165	d1,2	Et	2,4-di-Cl-Ph	597	APCI
166	d1,2	Et	2,4-F-Ph	566	APCI
167	d1	Et	4-CF ₃ -Ph	598	APCI
168	d1,2	Et	4-CF ₃ -Ph	598	APCI
169	d1	Et	4-Cl-Ph	563	PB
170	d2	Et	4-Cl-Ph	563	PB
171	d1,2	Et	4-F-Ph	547	APCI
172	d1,2	Et	4-Me-Ph	543	APCI
173	d1,2	CF ₃ CH ₂	2,4-di-Cl-Ph	651.5	APCI
174	d1,2	CF ₃ CH ₂	2,4-di-F-Ph	620	APCI
175	d1	CF ₃ CH ₂	4-Cl-Ph	617	PB
176	d2	CF ₃ CH ₂	4-Cl-Ph	617	PB
177	d1	CF ₃ CH ₂	4-F-Ph	601	APCI
178	d2	CF ₃ CH ₂	4-F-Ph	601	APCI
179	d1,2	CF ₃ CH ₂	4-Me-Ph	597	APCI

Note: in the above table, the isomer designation refers to the stereochemistry at the C-3 position (indicated by the "*" in the structure) of the pyrazalone-piperidine group; d1 and d2 refer to isomers that were chromatographically separated; d1,2 refers to a mixture of isomers.

5

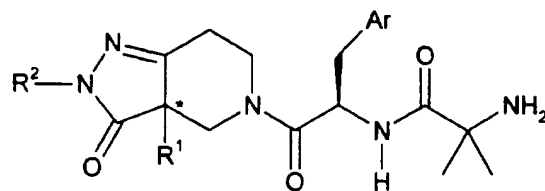
Examples 180 - 183

Examples 180 to 183 shown in the table below were prepared according to the scheme illustrated below by coupling the appropriately substituted pyrazalone-piperidine I with the acid intermediate IV in an analogous manner to the procedures described in Examples 3E and 3F.



The acid intermediate (IV) was prepared by treating an amino acid with the product from Example 5D using the established procedure described in Example 5F.

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Ex. #	Isomer	R ²	R ¹ = -CH ₂ -A ¹	Ar	MS	Method
180	d1,2	Me	Phenyl	(CH ₂) ₂ Ph	504	PB
181	d1,2	Me	Phenyl	SCH ₂ Ph	559	PB
182	d1	Me	Phenyl	2-Naphthalenyl	527	APCI
183	d1,2	Me	Phenyl	CH ₂ O-(4-F-Ph)	524	PB

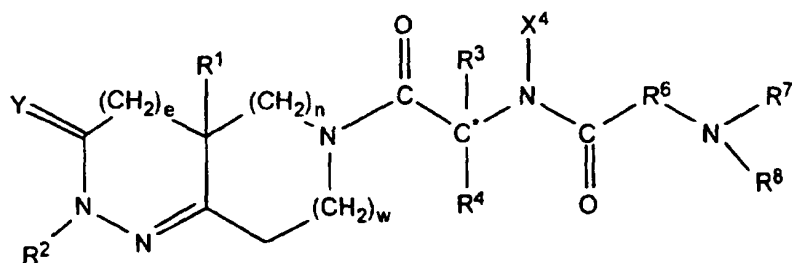
Note: in the above table, the isomer designation refers to the stereochemistry at the C-3 position (indicated by the "*" in the structure) of the pyrazalone-piperidine group;

- 5 d1 and d2 refer to isomers that were chromatographically separated; d1,2 refers to a mixture of isomers.

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CLAIMS

1. A compound of the formula



(1)

- 5 the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts and prodrugs thereof,

wherein

e is 0 or 1:

n and w are each independently 0, 1 or 2;

- 10 provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, $-CN$, $-(CH_2)_6N(X^6)C(O)X^6$, $-(CH_2)_6N(X^6)C(O)(CH_2)_4-A^1$.

$$-(\text{CH}_2)_6\text{N}(\text{X}^6)\text{SO}_2(\text{CH}_2)_t\text{A}^1, -(\text{CH}_2)_6\text{N}(\text{X}^6)\text{SO}_2\text{X}^6, -(\text{CH}_2)_6\text{N}(\text{X}^6)\text{C}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_t\text{A}^1,$$
$$-(\text{CH}_2)_6\text{N}(\text{X}^6)\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6), -(\text{CH}_2)_6\text{C}(\text{O})\text{N}(\text{X}^6)(\text{X}^6), -(\text{CH}_2)_6\text{C}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_t\text{A}^1,$$

- 15 $-(\text{CH}_2)_n\text{C}(\text{O})\text{OX}^6$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{O}(\text{CH}_2)_r\text{A}^1$, $-(\text{CH}_2)_n\text{OX}^6$, $-(\text{CH}_2)_n\text{OC}(\text{O})\text{X}^6$,

$$-(\text{CH}_2)_6\text{OC}(\text{O})(\text{CH}_2)_7\text{A}^1, -(\text{CH}_2)_6\text{OC}(\text{O})\text{N}(\text{X}^6)(\text{CH}_2)_7\text{A}^1, -(\text{CH}_2)_6\text{OC}(\text{O})\text{N}(\text{X}^6)(\text{X}^6),$$
$$-(\text{CH}_2)_n\text{C}(\text{O})\text{X}^6, -(\text{CH}_2)_n\text{C}(\text{O})(\text{CH}_2)_l\text{A}^1, -(\text{CH}_2)_n\text{N}(\text{X}^6)\text{C}(\text{O})\text{OX}^6,$$
$$-(\text{CH}_2)_a\text{N}(\text{X}^6)\text{SO}_2\text{N}(\text{X}^6)(\text{X}^6), -(\text{CH}_2)_a\text{S}(\text{O})_m\text{X}^6, -(\text{CH}_2)_a\text{S}(\text{O})_m(\text{CH}_2)_l\text{A}^1,$$

- (C_1-C_{10}) alkyl, $-(CH_2)_1-A^1$, $-(CH_2)_0-(C_3-C_7)$ cycloalkyl, $-(CH_2)_0-Y^1-(C_1-C_6)$ alkyl,

- 20 $-(\text{CH}_2)_n\text{-Y}^1\text{-(CH}_2)_l\text{-A}^1$ or $-(\text{CH}_2)_n\text{-Y}^1\text{-(CH}_2)_l\text{-(C}_3\text{-C}_7\text{)cycloalkyl}$;

where the alkyl and cycloalkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, -CONH₂,

-S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1, 2 or 3 fluoro;

Y¹ is O, S(O)_m, -C(O)NX⁶-, -CH=CH-, -C≡C-, -N(X⁶)C(O)-, -C(O)NX⁶-,

- 25 $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

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said $(CH_2)_q$ group and $(CH_2)_l$ group may each be optionally substituted with hydroxyl, (C_1-C_4) alkoxy, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl, $-CO_2(C_1-C_4)$ alkyl ester, 1H-tetrazol-5-yl, 1, 2 or 3 fluoro, or 1 or 2 (C_1-C_4) alkyl;

- 5 R^2 is hydrogen, (C_1-C_8) alkyl, $-(C_0-C_3)$ alkyl- (C_3-C_8) cycloalkyl, $-(C_1-C_4)$ alkyl- A^1 or A^1 ; where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1, 2 or 3 halogen;

- R^3 is A^1 , (C_1-C_{10}) alkyl, $-(C_1-C_6)$ alkyl- A^1 , $-(C_1-C_6)$ alkyl- (C_3-C_7) cycloalkyl,
10 $-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl, $-(C_1-C_5)$ alkyl- X^1 - (C_0-C_5) alkyl- A^1 or $-(C_1-C_5)$ alkyl- X^1 - (C_1-C_5) alkyl- (C_3-C_7) cycloalkyl;

where the alkyl groups in the definition of R^3 are optionally substituted with

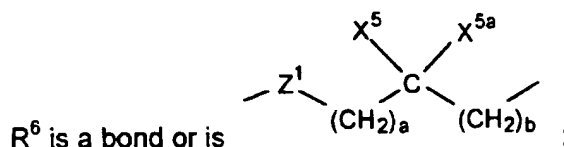
$-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1, 2, 3, 4 or 5 halogens, or 1, 2 or 3 OX^3 ;

X^1 is O, $S(O)_m$, $-N(X^2)C(O)-$, $-C(O)N(X^2)-$, $-OC(O)-$, $-C(O)O-$, $-CX^2=CX^2-$,

- 15 $-N(X^2)C(O)O-$, $-OC(O)N(X^2)-$ or $-C\equiv C-$;

R^4 is hydrogen, (C_1-C_6) alkyl or (C_3-C_7) cycloalkyl, or R^4 is taken together with R^3 and the carbon atom to which they are attached and form (C_5-C_7) cycloalkyl, (C_5-C_7) cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen,
20 sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

X^4 is hydrogen or (C_1-C_6) alkyl or X^4 is taken together with R^4 and the nitrogen atom
25 to which X^4 is attached and the carbon atom to which R^4 is attached and form a five to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X^5 and X^{5a} are each independently selected from the group consisting of hydrogen, trifluoromethyl, A^1 and optionally substituted (C_1-C_6) alkyl;

30

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the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is optionally substituted with a substituent selected from the group consisting of A¹, OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

5 or the carbon bearing X⁵ or X^{5a} forms one or two alkylene bridges with the nitrogen atom bearing R⁷ and R⁸ wherein each alkylene bridge contains 1 to 5 carbon atoms, provided that when one alkylene bridge is formed then X⁵ or X^{5a} but not both may be on the carbon atom and R⁷ or R⁸ but not both may be on the nitrogen atom and further provided that when two alkylene bridges
10 are formed then X⁵ and X^{5a} cannot be on the carbon atom and R⁷ and R⁸ cannot be on the nitrogen atom;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a partially saturated or fully saturated 3- to 7-membered ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1
15 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms
20 independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

Z¹ is a bond, O or N-X², provided that when a and b are both 0 then Z¹ is not
25 N-X² or O;

R⁷ and R⁸ are independently hydrogen or optionally substituted (C₁-C₆)alkyl;

where the optionally substituted (C₁-C₆)alkyl in the definition of R⁷ and R⁸ is optionally independently substituted with A¹, -C(O)O-(C₁-C₆)alkyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 -O-C(O)(C₁-
30 C₁₀)alkyl or 1 to 3 (C₁-C₆)alkoxy; or

R⁷ and R⁸ can be taken together to form -(CH₂)_r-L-(CH₂)_r;

where L is C(X²)(X²), S(O)_m or N(X²);

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A¹ for each occurrence is independently (C₅-C₇)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶, -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl, -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶), -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

where L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

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X^2 for each occurrence is independently hydrogen, optionally substituted (C_1 - C_6)alkyl, or optionally substituted (C_3 - C_7)cycloalkyl, where the optionally substituted (C_1 - C_6)alkyl and optionally substituted (C_3 - C_7)cycloalkyl in the definition of X^2 are optionally independently substituted with $-S(O)_m(C_1-C_6)$ alkyl, $-C(O)OX^3$, 1 to 5

5 halogens or 1-3 OX^3 ;

X^3 for each occurrence is independently hydrogen or (C_1 - C_6)alkyl;

X^6 is independently hydrogen, optionally substituted (C_1 - C_6)alkyl, (C_2 - C_6)halogenated alkyl, optionally substituted (C_3 - C_7)cycloalkyl, (C_3 - C_7)-halogenatedcycloalkyl, where optionally substituted (C_1 - C_6)alkyl and optionally substituted (C_3 - C_7)cycloalkyl in the

10 definition of X^6 is optionally independently substituted by 1 or 2 (C_1 - C_4)alkyl, hydroxyl, (C_1 - C_4)alkoxy, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)$ alkyl, carboxylate (C_1 - C_4)alkyl ester, or 1H-tetrazol-5-yl; or

when there are two X^6 groups on one atom and both X^6 are independently (C_1 - C_6)alkyl, the two (C_1 - C_6)alkyl groups may be optionally joined and, together with the
15 atom to which the two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or (C_1 - C_6)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

20 X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

when R^6 is a bond then L is $N(X^2)$ and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is independently 2 or 3.

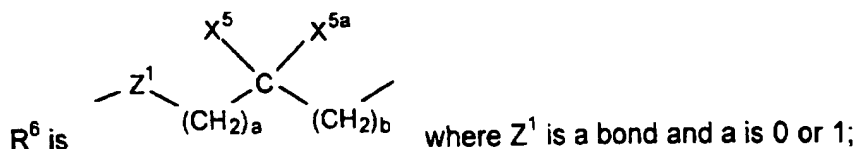
2. A compound according to claim 1 wherein

25 X^4 is hydrogen;

R^4 is hydrogen or methyl;

R^7 is hydrogen or (C_1 - C_3)alkyl;

R^8 is hydrogen or (C_1 - C_3)alkyl optionally substituted with one or two hydroxyl groups;



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X^5 and X^{5a} are each independently hydrogen, trifluoromethyl, phenyl, or optionally substituted (C_1-C_6) alkyl;

where the optionally substituted (C_1-C_6) alkyl is optionally substituted with OX^2 , imidazolyl, phenyl, indolyl, p-hydroxyphenyl, (C_5-C_7) cycloalkyl,

5 $-S(O)_m(C_1-C_6)$ alkyl, $-N(X^2)(X^2)$ or $-C(O)N(X^2)(X^2)$;

or X^5 and R^7 are taken together to form a (C_1-C_5) alkylene bridge.

3. A compound according to claim 2 wherein b is 0; X^5 and X^{5a} are each independently hydrogen, (C_1-C_3) alkyl or hydroxy (C_1-C_3) alkyl;

R^3 is selected from the group consisting of 1-indolyl- CH_2- , 2-indolyl- CH_2- , 3-indolyl-
10 CH_2- , 1-naphthyl- CH_2- , 2-naphthyl- CH_2- , 1-benzimidazolyl- CH_2- , 2-benzimidazolyl-
 CH_2- , phenyl- (C_1-C_4) alkyl-, 2-pyridyl- (C_1-C_4) alkyl-, 3-pyridyl- (C_1-C_4) alkyl-, 4-pyridyl-
 (C_1-C_4) alkyl-, phenyl- CH_2-S-CH_2- , thienyl- (C_1-C_4) alkyl-, phenyl- (C_0-C_3) alkyl-O- CH_2- ,
phenyl- CH_2-O -phenyl- CH_2- and 3-benzothienyl- CH_2- ;

where the aryl portion(s) of the groups defined for R^3 are optionally
15 substituted with one to three substituents, each substituent being
independently selected from the group consisting of methylenedioxy, F, Cl,
 CH_3 , OCH_3 , OCF_3 , OCF_2H and CF_3 .

4. A compound according to claim 3 wherein

R^4 is hydrogen;

20 a is 0;

n is 1 or 2;

w is 0 or 1;

X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided
that when X^5 is hydrogen then X^{5a} is not hydrogen;

25 R^7 and R^8 are each hydrogen; and

R^3 is phenyl- CH_2-O-CH_2- , phenyl- CH_2-S-CH_2- , 1-naphthyl- CH_2- , 2-naphthyl- CH_2- ,
phenyl- $(CH_2)_3-$ or 3-indolyl- CH_2- ;

where the aryl portion of the groups defined for R^3 is optionally substituted
with one to three substituents, each substituent being independently selected
30 from the group consisting of fluoro, chloro, methyl, OCH_3 , OCF_2H , OCF_3 and
 CF_3 .

5. A compound according to claim 4 wherein

R^1 is $-(CH_2)_l-A^1$, $-(CH_2)_q-(C_3-C_7)$ cycloalkyl or (C_1-C_{10}) alkyl;

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where A¹ in the definition of R¹ is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of fluoro, chloro, methyl, OCH₃, OCF₂H, OCF₃ and CF₃;

the cycloalkyl and alkyl groups in the definition of R¹ are optionally substituted with (C₁-C₄)alkyl, hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂,
 -S(O)_m(C₁-C₆)alkyl, -CO₂(C₁-C₄)alkyl ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;

Y is O;

R² is hydrogen, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, phenyl or (C₁-C₈)alkyl where the (C₁-C₈)alkyl group is optionally substituted with hydroxyl, -CF₃ or 1 to 3 halogen.

6. A compound according to claim 5 wherein w is 0 and n is 1.

7. A compound according to claim 5 wherein e is 0; n and w are each 1;
 R¹ is -(CH₂)_t-A¹;

where A¹ in the definition of R¹ is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents,

each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H;

t is 0, 1 or 2;

and R³ is phenyl-CH₂-O-CH₂-, phenyl-(CH₂)₃- or 3-indolyl-CH₂-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H.

8. A compound according to claim 7 wherein X⁵ and X^{5a} are each methyl; R¹ is -CH₂-phenyl, -CH₂-4-fluoro-phenyl, -CH₂-pyridyl or -CH₂-thiazolyl and R² is hydrogen, methyl, ethyl, t-butyl or -CH₂CF₃.

9. A compound according to claim 8 wherein R¹ is -CH₂-phenyl and R³ is phenyl-(CH₂)₃-.

10. The diastereomeric mixture of a compound according to claim 9 where said compound is 2-amino-N-[1-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide.

11. The compound according to claim 10 where the compound is 2-amino-N-[1-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide.

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12. The compound according to claim 10 where the compound is 2-amino-N-[1-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridine-5-carbonyl)-4-phenyl-(R)-butyl]-isobutyramide.

13. A compound according to claim 8 wherein R¹ is -CH₂-phenyl or -CH₂-4-fluoro-phenyl and R³ is 3-indolyl-CH₂-.

14. The diastereomeric mixture of a compound according to claim 13 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

15. The compound according to claim 14 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

16. The compound according to claim 14 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

17. The diastereomeric mixture of a compound according to claim 13 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

18. The compound according to claim 17 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

19. The compound according to claim 17 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

20. The diastereomeric mixture of a compound according to claim 13 where said compound is 2-amino-N-[2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

21. The compound according to claim 20 where the compound is 2-amino-N-[2-[3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.

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22. The compound according to claim 20 where the compound is 2-amino-N-[2-[3a-(S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-(1H-indol-3-ylmethyl)-2-oxo-ethyl]-isobutyramide.
23. A compound according to claim 8 wherein R¹ is -CH₂-phenyl or
5 -CH₂-4-fluoro-phenyl and R³ is phenyl-CH₂-O-CH₂-.
24. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.
- 10 25. The compound according to claim 24 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.
26. The compound according to claim 25 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-
15 c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide L-tartaric acid salt.
27. The compound according to claim 24 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo-[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.
28. The diastereomeric mixture of a compound according to claim 23
20 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.
29. The compound according to claim 28 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-
25 c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.
30. The compound according to claim 28 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-ethyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.
31. The diastereomeric mixture of a compound according to claim 23
30 where said compound is 2-amino-N-[2-[3a-(R,S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

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32. The compound according to claim 31 where the compound is 2-amino-N-{2-[3a-(R)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-isobutyramide.

33. The compound according to claim 31 where the compound is 2-amino-N-{2-[3a-(S)-benzyl-3-oxo-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-1-(R)-benzyloxymethyl-2-oxo-ethyl}-isobutyramide.

34. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(R,S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide.

35. The compound according to claim 34 where the compound is 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(R)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide.

36. The compound according to claim 34 where the compound is 2-amino-N-{1-(R)-benzyloxymethyl-2-[3a-(S)-(4-fluoro-benzyl)-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-2-oxo-ethyl}-isobutyramide.

37. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

38. The compound according to claim 37 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

39. The compound according to claim 37 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-tert-butyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

40. A compound according to claim 5 wherein e is 1; n is 1; w is 1; R^1 is $-(CH_2)_t-A^1$;

where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ;
t is 0, 1 or 2;

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and R³ is phenyl-CH₂-O-CH₂-, phenyl-(CH₂)₃- or 3-indolyl-CH₂-, where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H.

5 41. A compound according to claim 40 wherein X⁵ and X^{5a} are each methyl; R¹ is -CH₂-phenyl, -CH₂-4-fluoro-phenyl, -CH₂-pyridyl or -CH₂-thiazolyl and R² is hydrogen, methyl, ethyl, t-butyl or -CH₂CF₃.

 42. The diastereomeric mixture of a compound according to claim 23 where said compound is 2-amino-N-[2-(3a-(R,S)-benzyl-3-oxo-2,3,3a,4,6,7-
10 hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

 43. A compound according to claim 42 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

15 44. A compound according to claim 42 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-1-(R)-benzyloxymethyl-2-oxo-ethyl]-isobutyramide.

 45. A method for increasing levels of endogenous growth hormone in a human or other animal which comprises administering to such human or animal an
20 effective amount of a compound of claim 1.

 46. A pharmaceutical composition useful for increasing the endogenous production or release of growth hormone in a human or other animal which comprises an inert carrier and an effective amount of a compound of claim 1.

 47. A pharmaceutical composition useful for increasing the endogenous
25 production or release of growth hormone in a human or other animal which comprises an inert carrier, an effective amount of a compound of claim 1 and a growth hormone secretagogue selected from the group consisting of GHRP-6, Hexarelin, GHRP-1, growth hormone releasing factor (GRF), IGF-1, IGF-2 and B-HT920 or an analog thereof.

30 48. A method for treating or preventing osteoporosis which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in treating or preventing osteoporosis.

49. A method for treating or preventing diseases or conditions which may be treated or prevented by growth hormone which comprises administering to a human or other animal in need of such treatment or prevention an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.
50. A method according to claim 49 wherein the disease or condition is congestive heart failure, frailty associated with aging or obesity.
51. A method for accelerating bone fracture repair, attenuating protein catabolic response after a major operation, reducing cachexia and protein loss due to chronic illness, accelerating wound healing, or accelerating the recovery of burn patients or patients having undergone major surgery, which method comprises administering to a mammal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.
52. A method for improving muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis or renal homeostasis, which method comprises administering to a human or other animal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.
53. A method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of a bisphosphonate compound and a compound of claim 1.
54. A method for the treatment of osteoporosis according to claim 53 wherein the bisphosphonate compound is alendronate.
55. A method for the treatment or prevention of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of estrogen or Premarin® and a compound of claim 1 and optionally progesterone.
56. A compound according to claim 2 wherein b is 0; X^5 and X^{5a} are each independently hydrogen, (C₁-C₃)alkyl or hydroxy(C₁-C₃)alkyl; R^3 is selected from the group consisting of 1-indolyl-CH₂-, 2-indolyl-CH₂-, 3-indolyl-CH₂-, 1-naphthyl-CH₂-, 2-naphthyl-CH₂-, 1-benzimidazolyl-CH₂-, 2-benzimidazolyl-CH₂-, phenyl-(C₁-C₄)alkyl-, 2-pyridyl-(C₁-C₄)alkyl-, 3-pyridyl-(C₁-C₄)alkyl-, 4-pyridyl-(C₁-C₄)alkyl-, phenyl-CH₂-S-CH₂-, thienyl-(C₁-C₄)alkyl-, phenyl-(C₀-C₃)alkyl-O-CH₂-,

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phenyl-CH₂-O-phenyl-CH₂-, 3-benzothieryl-CH₂-, thienyl-CH₂-O-CH₂-, thiazolyl-CH₂-O-CH₂-, pyridyl-CH₂-O-CH₂-, pyrimidyl-CH₂-O-CH₂- and phenyl-O-CH₂-CH₂;

where the aryl portion(s) of the groups defined for R³ are optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of methylenedioxy, F, Cl, CH₃, OCH₃, OCF₃, OCF₂H and CF₃.

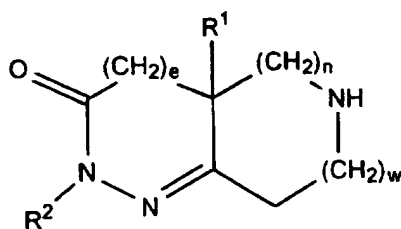
57. A method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of calcitonin and a compound of claim 1.

58. A method to increase IGF-1 levels in a human or other animal deficient in IGF-1 which comprises administering to a human or other animal with IGF-1 deficiency a compound of claim 1.

59. A method for the treatment of osteoporosis which comprises administering to a human or other animal with osteoporosis a combination of an estrogen agonist or antagonist and a compound of claim 1.

60. A method according to claim 59 wherein the estrogen agonist or antagonist is tamoxifen, droloxifene, raloxifene or idoxifene.

61. A compound of the formula



(II)

the racemic-diastereomeric mixtures and optical isomers of said compounds and the pharmaceutically-acceptable salts thereof, wherein

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at

the same time;

R¹ is hydrogen, -CN, -(CH₂)_qN(X⁶)C(O)X⁶, -(CH₂)_qN(X⁶)C(O)(CH₂)_r-A¹, -(CH₂)_qN(X⁶)SO₂(CH₂)_r-A¹, -(CH₂)_qN(X⁶)SO₂X⁶, -(CH₂)_qN(X⁶)C(O)N(X⁶)(CH₂)_r-A¹, -(CH₂)_qN(X⁶)C(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(X⁶), -(CH₂)_qC(O)N(X⁶)(CH₂)_r-A¹,

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- $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_tA^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$,
 $-(CH_2)_qOC(O)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_tA^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,
 $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_tA^1$, $-(CH_2)_qN(X^6)C(O)OX^6$,
 $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_tA^1$,
5 $-(C_1-C_{10})alkyl$, $-(CH_2)_tA^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_qY^1-(C_1-C_6)alkyl$,
 $-(CH_2)_qY^1-(CH_2)_tA^1$ or $-(CH_2)_qY^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;
where the alkyl and cycloalkyl groups in the definition of R^1 are optionally
substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $CONH_2$,
 $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$, 1H-tetrazol-5-yl or 1 to 3 fluoro;
10 Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)-$, $-C(O)NX^6-$,
 $-C(O)O-$, $-OC(O)N(X^6)-$ or $-OC(O)-$;
 q is 0, 1, 2, 3 or 4;
 t is 0, 1, 2 or 3;
said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with 1
15 to 3 fluoro, 1 or 2 $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$,
 $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$ ester, or 1H-tetrazol-5-yl;
 R^2 is hydrogen, $(C_1-C_8)alkyl$, $-(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkylA^1$ or A^1 ;
where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally
substituted by hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)alkyl$,
20 $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1 to 3 halogen;
 A^1 for each occurrence is independently $(C_5-C_7)cycloalkenyl$, phenyl or a partially
saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally
having 1 to 4 heteroatoms independently selected from the group consisting of
oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially
25 saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally
having 1 to 4 heteroatoms independently selected from the group consisting of
nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully
unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms
independently selected from the group consisting of nitrogen, sulfur and oxygen;
30 A^1 for each occurrence is independently optionally substituted, in one or
optionally both rings if A^1 is a bicyclic ring system, with up to three
substituents, each substituent independently selected from the group
consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$,

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- C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl,
 -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy,
 halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶),
 -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,
 5 -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and
 tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy
 then it can only be substituted by one methylenedioxy;
 where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;
 the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is
 10 optionally independently substituted with phenyl, phenoxy, (C₁-
 C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3
 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;
 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or
 thienyl, provided that when X¹² is not hydrogen, X¹² is optionally
 15 substituted with one to three substituents independently selected from
 the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;
 or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;
 L¹ is C(X²)(X²), O, S(O)_m or N(X²);
 r for each occurrence is independently 1, 2 or 3;
 20 X² for each occurrence is independently hydrogen, optionally substituted (C₁-
 C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted
 (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are
 optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5
 halogens or 1 to 3 OX³;
 25 X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;
 X⁶ for each occurrence is independently hydrogen, optionally substituted (C₁-
 C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, or (C₃-
 C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally
 substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently
 30 substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl,
 -CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl or 1 or 2 (C₁-C₄)alkyl; or
 where there are two X⁶ groups on one atom and both X⁶ are (C₁-C₆)alkyl, the two
 (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the

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two X^6 groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX^7 ;

X^7 is hydrogen or (C_1-C_6) alkyl optionally substituted with hydroxyl; and m for each occurrence is independently 0, 1 or 2;

5 with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to $C(O)$ or SO_2 in the form $C(O)X^6$, $C(O)X^{12}$, SO_2X^6 or SO_2X^{12} ; and

when R^2 is hydrogen then R^1 is not $-CH=CH$ -phenyl.

62. A compound according to claim 61 wherein

10 w is 0 or 1;

n is 1;

R^1 is hydrogen, $-(CH_2)_q-(C_3-C_7)$ cycloalkyl, $-(CH_2)_l-A^1$ or (C_1-C_{10}) alkyl where the (C_1-C_{10}) alkyl and (C_3-C_7) cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A^1 in the definition of R^1 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, methoxy, CF_3 , OCF_3 and OCF_2H ;

15 R^2 is hydrogen, (C_1-C_8) alkyl, (C_0-C_3) alkyl- (C_3-C_7) cycloalkyl, phenyl, or (C_1-C_3) alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF_3 , OH and methoxy.

20 63. A compound according to claim 62 wherein w is 1; e is 0; R^1 is $-CH_2$ -pyridyl, $-CH_2$ -thiazolyl, or $-CH_2$ -phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R^2 is hydrogen, (C_1-C_4) alkyl or phenyl where the (C_1-C_4) alkyl or phenyl groups in the definition of R^2 is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy or methoxy.

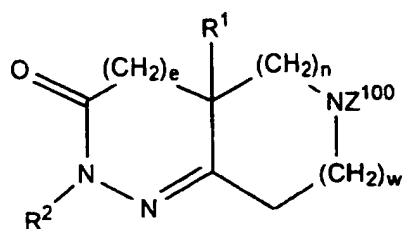
64. A compound according to claim 63 wherein R^1 is $-CH_2$ -phenyl and R^2 is methyl or hydrogen.

65. A compound according to claim 64 wherein the compound is the 3a-
30 (R) enantiomer.

66. A compound according to claim 64 wherein the compound is the 3a-
(S) enantiomer.

67. A compound of the formula

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(III)

the racemic-diastereomeric mixtures and optical isomers of said compounds, wherein

- 5 Z^{100} is methyl, BOC, CBZ, $CF_3C(O)-$, FMOC, TROC, trityl, tosyl, $CH_3C(O)-$ or optionally substituted benzyl which is optionally substituted with methoxy, dimethoxy or nitro;

e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at

- 10 the same time;

R^1 is hydrogen, $-CN$, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$, $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$, $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$, $-(C_1-C_{10})alkyl$, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$, $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;

- 20 where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $CONH_2$, $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$, 1H-tetrazol-5-yl or 1 to 3 fluoro; Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)$, $-C(O)NX^6$, $-C(O)O$, $-OC(O)N(X^6)$ or $-OC(O)$;

- 25 q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$,

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-CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 (C₁-C₄)alkyl;

R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₈)cycloalkyl, -(C₁-C₄)alkyl-A¹ or A¹;

where the alkyl groups and the cycloalkyl groups in the definition of R² are optionally substituted with hydroxyl, -C(O)OX⁶, -C(O)N(X⁶)(X⁶), -N(X⁶)(X⁶), -S(O)_m(C₁-C₆)alkyl,

5 -C(O)A¹, -C(O)(X⁶), CF₃, CN or 1 to 3 halogen;

A¹ for each occurrence is independently (C₅-C₇)cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

15 A¹ for each occurrence is independently optionally substituted, in one or optionally both rings if A¹ is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group consisting of F, Cl, Br, I, OCF₃, OCF₂H, CF₃, CH₃, OCH₃, -OX⁶, -C(O)N(X⁶)(X⁶), -C(O)OX⁶, oxo, (C₁-C₆)alkyl, nitro, cyano, benzyl, 20 -S(O)_m(C₁-C₆)alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, -N(X⁶)(X⁶), -N(X⁶)C(O)(X⁶), -SO₂N(X⁶)(X⁶), -N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹², -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy then it can only be substituted with one methylenedioxy;

25 where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is optionally independently substituted with phenyl, phenoxy, (C₁-C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;

30 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or thienyl, provided that when X¹² is not hydrogen, X¹² is optionally

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substituted with one to three substituents independently selected from the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;

or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;

L¹ is C(X²)(X²), O, S(O)_m or N(X²);

5 r for each occurrence is independently 1, 2 or 3;

X² for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5

10 halogens or 1 to 3 OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

X⁶ for each occurrence is independently hydrogen, optionally substituted (C₁-C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, or (C₃-C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally

15 substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl,

-CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl or 1 or 2 (C₁-C₄)alkyl; or

where there are two X⁶ groups on one atom and both X⁶ are (C₁-C₆)alkyl, the two (C₁-C₆)alkyl groups may be optionally joined and, together with the atom to which the
20 two X⁶ groups are attached, form a 4- to 9- membered ring optionally having oxygen, sulfur or NX⁷;

X⁷ is hydrogen or (C₁-C₆)alkyl optionally substituted with hydroxyl; and

m for each occurrence is independently 0, 1 or 2;

with the proviso that:

25 X⁶ and X¹² cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O)X⁶, C(O)X¹², SO₂X⁶ or SO₂X¹²;

when R² is hydrogen then R¹ is not -CH=CH-phenyl;

when R² is H and R¹ is -CH₂-CH=CH-Ph, then Z¹⁰⁰ is not BOC;

when R² is H and R¹ is then Z¹⁰⁰ is not BOC;

30 when R² is H and R¹ is -CH₂-C(CH₃)=CH₂, then Z¹⁰⁰ is not BOC; and

when R² is phenyl and R¹ is -CH₃, then Z¹⁰⁰ is not CH₃C(O)-.

68. A compound according to claim 67 wherein

w is 0 or 1;

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n is 1;

Z¹⁰⁰ is BOC, methyl, benzyl or CBZ;

R¹ is hydrogen, -(CH₂)_q-(C₃-C₇)cycloalkyl, -(CH₂)_t-A¹ or (C₁-C₁₀)alkyl where the (C₁-C₁₀)alkyl and (C₃-C₇)cycloalkyl groups are optionally substituted with 1 to 3 fluoro and A¹ in the definition of R¹ is optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H;

R² is hydrogen, (C₁-C₈)alkyl, -(C₀-C₃)alkyl-(C₃-C₇)cycloalkyl, phenyl, or -(C₁-C₃)alkyl-phenyl where the alkyl and phenyl groups are optionally substituted with 1 to 3 substituents independently selected from the group consisting of F, CF₃, OH and OMe.

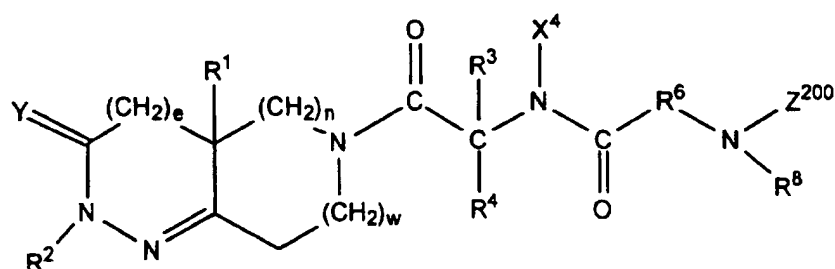
69. A compound according to claim 68 wherein Z¹⁰⁰ is BOC; w is 1; e is 0; R¹ is -CH₂-pyridyl, -CH₂-thiazolyl, or -CH₂-phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro and chloro; and R² is hydrogen, (C₁-C₄)alkyl or phenyl where the (C₁-C₄)alkyl or phenyl groups in the definition of R² is optionally substituted with 1 to 3 substituents independently selected from the group consisting of fluoro, hydroxy or methoxy.

70. A compound according to claim 69 wherein R¹ is -CH₂-phenyl and R² is methyl or hydrogen.

71. A compound according to claim 70 wherein the compound is the 3a-(R) enantiomer.

72. A compound according to claim 70 wherein the compound is the 3a-(S) enantiomer.

73. A compound of the formula



(IV)

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the racemic-diastereomeric mixtures and optical isomers of said compounds, wherein

Z^{200} is t-BOC, CBZ, $CF_3C(O)-$, Fmoc, TROC, trityl, tosyl or optionally substituted benzyl which is optionally substituted with methoxy, dimethoxy or nitro;

5 e is 0 or 1;

n and w are each independently 0, 1 or 2, provided that w and n cannot both be 0 at the same time;

Y is oxygen or sulfur;

R^1 is hydrogen, -CN, $-(CH_2)_qN(X^6)C(O)X^6$, $-(CH_2)_qN(X^6)C(O)(CH_2)_t-A^1$,

10 $-(CH_2)_qN(X^6)SO_2(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)SO_2X^6$, $-(CH_2)_qN(X^6)C(O)N(X^6)(CH_2)_t-A^1$,
 $-(CH_2)_qN(X^6)C(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(X^6)$, $-(CH_2)_qC(O)N(X^6)(CH_2)_t-A^1$,
 $-(CH_2)_qC(O)OX^6$, $-(CH_2)_qC(O)O(CH_2)_t-A^1$, $-(CH_2)_qOX^6$, $-(CH_2)_qOC(O)X^6$,
 $-(CH_2)_qOC(O)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(CH_2)_t-A^1$, $-(CH_2)_qOC(O)N(X^6)(X^6)$,
 $-(CH_2)_qC(O)X^6$, $-(CH_2)_qC(O)(CH_2)_t-A^1$, $-(CH_2)_qN(X^6)C(O)OX^6$,
 15 $-(CH_2)_qN(X^6)SO_2N(X^6)(X^6)$, $-(CH_2)_qS(O)_mX^6$, $-(CH_2)_qS(O)_m(CH_2)_t-A^1$,
 $-(C_1-C_{10})alkyl$, $-(CH_2)_t-A^1$, $-(CH_2)_q-(C_3-C_7)cycloalkyl$, $-(CH_2)_q-Y^1-(C_1-C_6)alkyl$,
 $-(CH_2)_q-Y^1-(CH_2)_t-A^1$ or $-(CH_2)_q-Y^1-(CH_2)_t-(C_3-C_7)cycloalkyl$;

where the alkyl and cycloalkyl groups in the definition of R^1 are optionally substituted with $(C_1-C_4)alkyl$, hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $CONH_2$,

20 $-S(O)_m(C_1-C_6)alkyl$, $-CO_2(C_1-C_4)alkyl$ ester, 1H-tetrazol-5-yl or 1 to 3 fluoro;
 Y^1 is O, $S(O)_m$, $-C(O)NX^6$, $-CH=CH-$, $-C\equiv C-$, $-N(X^6)C(O)$, $-C(O)NX^6$,
 $-C(O)O$, $-OC(O)N(X^6)$ or $-OC(O)$;

q is 0, 1, 2, 3 or 4;

t is 0, 1, 2 or 3;

25 said $(CH_2)_q$ group and $(CH_2)_t$ group may each be optionally substituted with hydroxyl, $(C_1-C_4)alkoxy$, carboxyl, $-CONH_2$, $-S(O)_m(C_1-C_6)alkyl$,
 $-CO_2(C_1-C_4)alkyl$, 1H-tetrazol-5-yl, 1 to 3 fluoro or 1 or 2 $(C_1-C_4)alkyl$;

R^2 is hydrogen, $(C_1-C_8)alkyl$, $-(C_0-C_3)alkyl-(C_3-C_8)cycloalkyl$, $-(C_1-C_4)alkyl-A^1$ or A^1 ;

where the alkyl groups and the cycloalkyl groups in the definition of R^2 are optionally

30 substituted with hydroxyl, $-C(O)OX^6$, $-C(O)N(X^6)(X^6)$, $-N(X^6)(X^6)$, $-S(O)_m(C_1-C_6)alkyl$,
 $-C(O)A^1$, $-C(O)(X^6)$, CF_3 , CN or 1 to 3 halogen;

R^3 is A^1 , $(C_1-C_{10})alkyl$, $-(C_1-C_6)alkyl-A^1$, $-(C_1-C_6)alkyl-(C_3-C_7)cycloalkyl$,

$-(C_1-C_5)alkyl-X^1-(C_1-C_5)alkyl$, $-(C_1-C_5)alkyl-X^1-(C_0-C_5)alkyl-A^1$ or

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-(C₁-C₅)alkyl-X¹-(C₁-C₅)alkyl-(C₃-C₇)cycloalkyl;

where the alkyl groups in the definition of R³ is optionally substituted with

-S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5 halogens or 1 to 3 OX³;

X¹ is O, S(O)_m, -N(X²)C(O)-, -C(O)N(X²)-, -OC(O)-, -C(O)O-, -CX²=CX²-,

5 -N(X²)C(O)O-, -OC(O)N(X²)- or -C≡C-;

R⁴ is hydrogen, (C₁-C₆)alkyl or (C₃-C₇)cycloalkyl, or R⁴ is taken together with R³ and

the carbon atom to which they are attached and form (C₅-C₇)cycloalkyl, (C₅-

C₇)cycloalkenyl, a partially saturated or fully saturated 4- to 8-membered ring having

1 to 4 heteroatoms independently selected from the group consisting of oxygen,

10 sulfur and nitrogen, or is a bicyclic ring system consisting of a partially saturated or

fully saturated 5- or 6-membered ring, fused to a partially saturated, fully unsaturated

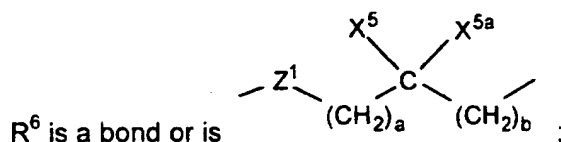
or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms

independently selected from the group consisting of nitrogen, sulfur and oxygen;

X⁴ is hydrogen or (C₁-C₆)alkyl or X⁴ is taken together with R⁴ and the nitrogen atom

15 to which X⁴ is attached and the carbon atom to which R⁴ is attached and form a five

to seven membered ring;



where a and b are independently 0, 1, 2 or 3;

X⁵ and X^{5a} are each independently selected from the group consisting of

20 hydrogen, trifluoromethyl, A¹ and optionally substituted (C₁-C₆)alkyl;

the optionally substituted (C₁-C₆)alkyl in the definition of X⁵ and X^{5a} is

optionally substituted with a substituent selected from the group

consisting of A¹, -OX², -S(O)_m(C₁-C₆)alkyl, -C(O)OX², (C₃-

C₇)cycloalkyl, -N(X²)(X²) and -C(O)N(X²)(X²);

25 or the carbon bearing X⁵ and X^{5a} forms an alkylene bridge with the nitrogen

atom bearing Z²⁰⁰ and R⁸ where the alkylene bridge contains 1 to 5 carbon

atoms provided that X⁵ or X^{5a} but not both may be on the carbon atom and

Z²⁰⁰ or R⁸ but not both may be on the nitrogen atom;

or X⁵ is taken together with X^{5a} and the carbon atom to which they are

30 attached and form a partially saturated or fully saturated 3- to 7-membered

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ring, or a partially saturated or fully saturated 4- to 8-membered ring having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen;

5 or X^5 is taken together with X^{5a} and the carbon atom to which they are attached and form a bicyclic ring system consisting of a partially saturated or fully saturated 5- or 6-membered ring, optionally having 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently
10 selected from the group consisting of nitrogen, sulfur and oxygen;

Z^1 is a bond, O or $N-X^2$, provided that when a and b are both 0 then Z^1 is not $N-X^2$ or O;

R^8 is hydrogen or optionally substituted (C_1-C_6) alkyl;

15 where the optionally substituted (C_1-C_6) alkyl in the definition of R^8 is optionally independently substituted with A^1 , $-C(O)O-(C_1-C_6)$ alkyl, $-S(O)_m(C_1-C_6)$ alkyl, 1 to 5 halogens, 1 to 3 hydroxy, 1 to 3 $-O-C(O)(C_1-C_{10})$ alkyl or 1 to 3 (C_1-C_6) alkoxy; or

A^1 for each occurrence is independently (C_5-C_7) cycloalkenyl, phenyl or a partially saturated, fully saturated or fully unsaturated 4- to 8-membered ring optionally
20 having 1 to 4 heteroatoms independently selected from the group consisting of oxygen, sulfur and nitrogen, or a bicyclic ring system consisting of a partially saturated, fully unsaturated or fully saturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of
25 nitrogen, sulfur and oxygen, fused to a partially saturated, fully saturated or fully unsaturated 5- or 6-membered ring, optionally having 1 to 4 heteroatoms independently selected from the group consisting of nitrogen, sulfur and oxygen;

A^1 for each occurrence is independently optionally substituted, in one or optionally both rings if A^1 is a bicyclic ring system, with up to three substituents, each substituent independently selected from the group
30 consisting of F, Cl, Br, I, OCF_3 , OCF_2H , CF_3 , CH_3 , OCH_3 , $-OX^6$, $-C(O)N(X^6)(X^6)$, $-C(O)OX^6$, oxo, (C_1-C_6) alkyl, nitro, cyano, benzyl, $-S(O)_m(C_1-C_6)$ alkyl, 1H-tetrazol-5-yl, phenyl, phenoxy, phenylalkyloxy, halophenyl, methylenedioxy, $-N(X^6)(X^6)$, $-N(X^6)C(O)(X^6)$, $-SO_2N(X^6)(X^6)$,

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-N(X⁶)SO₂-phenyl, -N(X⁶)SO₂X⁶, -CONX¹¹X¹², -SO₂NX¹¹X¹², -NX⁶SO₂X¹²,
 -NX⁶CONX¹¹X¹², -NX⁶SO₂NX¹¹X¹², -NX⁶C(O)X¹², imidazolyl, thiazolyl and
 tetrazolyl, provided that if A¹ is optionally substituted with methylenedioxy
 then it can only be substituted with one methylenedioxy;

- 5 where X¹¹ is hydrogen or optionally substituted (C₁-C₆)alkyl;
 the optionally substituted (C₁-C₆)alkyl defined for X¹¹ is
 optionally independently substituted with phenyl, phenoxy, (C₁-
 C₆)alkoxycarbonyl, -S(O)_m(C₁-C₆)alkyl, 1 to 5 halogens, 1 to 3
 hydroxy, 1 to 3 (C₁-C₁₀)alkanoyloxy or 1 to 3 (C₁-C₆)alkoxy;
 10 X¹² is hydrogen, (C₁-C₆)alkyl, phenyl, thiazolyl, imidazolyl, furyl or
 thienyl, provided that when X¹² is not hydrogen, X¹² is optionally
 substituted with one to three substituents independently selected from
 the group consisting of Cl, F, CH₃, OCH₃, OCF₃ and CF₃;
 or X¹¹ and X¹² are taken together to form -(CH₂)_r-L¹-(CH₂)_r;
 15 L¹ is C(X²)(X²), O, S(O)_m or N(X²);

r for each occurrence is independently 1, 2 or 3;

- X² for each occurrence is independently hydrogen, optionally substituted (C₁-
 C₆)alkyl, or optionally substituted (C₃-C₇)cycloalkyl, where the optionally substituted
 (C₁-C₆)alkyl and optionally substituted (C₃-C₇)cycloalkyl in the definition of X² are
 20 optionally independently substituted with -S(O)_m(C₁-C₆)alkyl, -C(O)OX³, 1 to 5
 halogens or 1 to 3 -OX³;

X³ for each occurrence is independently hydrogen or (C₁-C₆)alkyl;

- X⁶ for each occurrence is independently hydrogen, optionally substituted (C₁-
 C₆)alkyl, (C₂-C₆)halogenated alkyl, optionally substituted (C₃-C₇)cycloalkyl, or (C₃-
 25 C₇)-halogenatedcycloalkyl, where optionally substituted (C₁-C₆)alkyl and optionally
 substituted (C₃-C₇)cycloalkyl in the definition of X⁶ is optionally independently
 substituted with hydroxyl, (C₁-C₄)alkoxy, carboxyl, CONH₂, -S(O)_m(C₁-C₆)alkyl,
 -CO₂(C₁-C₄)alkyl, 1H-tetrazol-5-yl or 1 or 2 (C₁-C₄)alkyl; or
 when there are two X⁶ groups on one atom and both X⁶ are (C₁-C₆)alkyl, the two (C₁-
 30 C₆)alkyl groups may be optionally joined and, together with the atom to which the two
 X⁶ groups are attached, form a 4- to 9- membered ring optionally having oxygen,
 sulfur or NX⁷;

X⁷ is hydrogen or (C₁-C₆)alkyl optionally substituted by hydroxyl; and

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m for each occurrence is independently 0, 1 or 2;

with the proviso that:

X^6 and X^{12} cannot be hydrogen when it is attached to C(O) or SO₂ in the form C(O) X^6 , C(O) X^{12} , SO₂ X^6 or SO₂ X^{12} ; and

- 5 when R^6 is a bond then L is N(X^2) and each r in the definition $-(CH_2)_r-L-(CH_2)_r-$ is 2 or 3.

74. A compound according to claim 73 wherein e is 0; Y is O; R^1 is $-CH_2$ -phenyl; R^2 is methyl or hydrogen; n is 1; w is 1; R^3 is $-CH_2-O-CH_2$ -phenyl; R^4 is hydrogen; X^4 is hydrogen; R^6 is $-C(CH_3)_2-$; Z^{200} is BOC and R^8 is hydrogen.

- 10 75. A compound according to claim 56 wherein

R^4 is hydrogen; a is 0; n is 1; w is 1; e is 0;

X^5 and X^{5a} are each independently, hydrogen, methyl or hydroxymethyl, provided that when X^5 is hydrogen then X^{5a} is not hydrogen;

R^7 and R^8 are each hydrogen;

- 15 Y is oxygen;

R^2 is hydrogen, methyl, ethyl, propyl, i-propyl, t-butyl, $-CH_2CF_3$, CF_3 or $-CH_2$ -cyclopropyl;

R^1 is CH_2-A^1 ;

- 20 where A^1 in the definition of R^1 is phenyl, thienyl, thiazolyl, pyridyl or pyrimidyl which is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ; and

R^3 is phenyl- CH_2-O-CH_2- , phenyl- $(CH_2)_3-$, 3-indolyl- CH_2- , thienyl- CH_2-O-CH_2- , thiazolyl- CH_2-O-CH_2- , pyridyl- CH_2-O-CH_2- , pyrimidyl- CH_2-O-CH_2- or phenyl-O- CH_2-

- 25 CH_2 , where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H .

76. A compound according to claim 75

wherein X^5 and X^{5a} are each methyl;

- 30 R^2 is methyl, ethyl, or $-CH_2CF_3$;

A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF_3 , OCF_3 and OCF_2H ;

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R^3 is phenyl-CH₂-O-CH₂-, phenyl-(CH₂)₃- or thienyl-CH₂-O-CH₂- where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H.

5 77. A compound according to claim 75

wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH₂CF₃;

A^1 is 2-pyridyl or 3-pyridyl optionally substituted with one to two substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H;

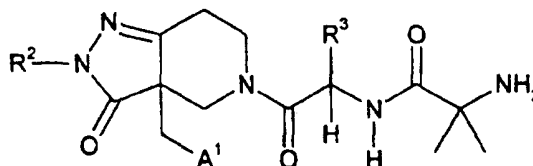
10 R^3 is phenyl-CH₂-O-CH₂-, phenyl-(CH₂)₃- or thienyl-CH₂-O-CH₂- where the aryl portion is optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H.

78. A compound according to claim 75

15 wherein X^5 and X^{5a} are each methyl; R^2 is methyl, ethyl, or CH₂CF₃;

A^1 is phenyl optionally substituted with one to three substituents, each substituent being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H; R^3 is 2-pyridyl-CH₂-O-CH₂-, or 3-pyridyl-CH₂-O-CH₂- where the aryl portion is optionally substituted with one to two substituents, each substituent
20 being independently selected from the group consisting of F, Cl, Me, OMe, CF₃, OCF₃ and OCF₂H.

79. A compound according to claim 77 having the formula



the racemic-diastereomeric mixtures and optical isomers of said compounds wherein

25 R^2 is methyl; A^1 is 2-pyridyl; and R^3 is -CH₂-O-CH₂-phenyl;

R^2 is CH₂CF₃; A^1 is 2-pyridyl; and R^3 is -CH₂-O-CH₂-3-chloro-phenyl;

R^2 is CH₂CF₃; A^1 is 2-pyridyl; and R^3 is -CH₂-O-CH₂-4-chloro-phenyl;

R^2 is CH₂CF₃; A^1 is 2-pyridyl; and R^3 is -CH₂-O-CH₂-2,4-di-chloro-phenyl;

R^2 is CH₂CF₃; A^1 is 2-pyridyl; and R^3 is -CH₂-O-CH₂-3-chloro-thiophene; or

R² is CH₂CF₃; A¹ is 2-pyridyl; and R³ is -CH₂-O-CH₂-2,4-di-fluoro-phenyl.

80. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide.

81. The compound according to claim 80 where the compound is 2-amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(R)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide.

82. The compound according to claim 80 where the compound is 2-Amino-N-[1-(R)-benzyloxymethyl-2-(2-methyl-3-oxo-3a-(S)-pyridin-2-ylmethyl-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl)-2-oxo-ethyl]-2-methyl-propionamide.

83. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

84. The compound according to claim 83 where the compound is 2-amino-N-{1-(R)-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

85. The compound according to claim 83 where the compound is 2-amino-N-{1-(R)-(3-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

86. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

87. The compound according to claim 86 where the compound is 2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

88. The compound according to claim 86 where the compound is 2-amino-N-{1-(R)-(4-chloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

5 89. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

10 90. The compound according to claim 89 where the compound is 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

15 91. The compound according to claim 89 where the compound is 2-amino-N-{1-(R)-(2,4-dichloro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

20 92. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide.

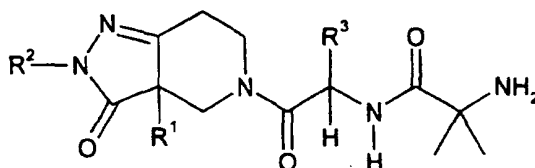
25 93. The compound according to claim 92 where the compound is 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide.

25 94. The compound according to claim 92 where the compound is 2-amino-N-{1-(R)-(4-chloro-thiophen-2-ylmethoxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,5,7-hexahydro-pyrazolo[3,4-c]pyridin-6-yl]-ethyl}-2-methyl-propionamide.

30 95. The diastereomeric mixture of a compound according to claim 79 where the compound is 2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R,S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.

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96. The compound according to claim 95 where the compound is 2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(R)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.
- 5 97. The compound according to claim 95 where the compound is 2-amino-N-{1-(R)-(2,4-difluoro-benzyloxymethyl)-2-oxo-2-[3-oxo-3a-(S)-pyridin-2-ylmethyl-2-(2,2,2-trifluoro-ethyl)-2,3,3a,4,6,7-hexahydro-pyrazolo[4,3-c]pyridin-5-yl]-ethyl}-2-methyl-propionamide.
98. A compound according to claim 8 having the formula



10

- the racemic-diastereomeric mixtures and optical isomers of said compounds wherein
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is $-(\text{CH}_2)_3\text{-phenyl}$;
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is 3-indolyl- $\text{CH}_2\text{-}$;
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is ethyl and R^3 is 3-indolyl- $\text{CH}_2\text{-}$;
- 15 R^1 is $-\text{CH}_2\text{-4-fluoro-phenyl}$, R^2 is methyl and R^3 is 3-indolyl- $\text{CH}_2\text{-}$;
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is ethyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is $-\text{CH}_2\text{CF}_3$ and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
- R^1 is $-\text{CH}_2\text{-4-fluoro-phenyl}$, R^2 is methyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$;
- 20 R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is t-butyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-phenyl}$; or
- R^1 is $-\text{CH}_2\text{-phenyl}$, R^2 is methyl and R^3 is $-\text{CH}_2\text{-O-CH}_2\text{-3,4-di-fluoro-phenyl}$.

99. The diastereomeric mixture of a compound according to claim 98 where the compound is 2-amino-N-[2-(3a-(R,S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo [4,3-c]pyridin-5-yl)-1-(R)-(3,4-difluoro-benzyloxymethyl)-2-oxo-ethyl]-2-methyl-propionamide.
- 25

100. The compound according to claim 99 where the compound is 2-amino-N-[2-(3a-(R)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo [4,3-c]pyridin-5-yl)-1-(R)-(3,4-difluoro-benzyloxymethyl)-2-oxo-ethyl]-2-methyl-propionamide.

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101. The compound according to claim 99 where the compound is 2-amino-N-[2-(3a-(S)-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydro-pyrazolo [4,3-c]pyridin-5-yl)-1-(R)-(3,4-difluoro-benzyloxymethyl)-2-oxo-ethyl]-2-methyl-propionamide.

5 102. A compound according to claim 41 wherein R¹ is -CH₂-phenyl; R² is hydrogen or methyl and R³ is -CH₂-O-CH₂-phenyl.

103. A method according to claim 50 wherein the disease or condition is congestive heart failure.

104. A method according to claim 50 wherein the disease or condition is
10 frailty associated with aging.

105. A method according to claim 51 wherein the method is for accelerating the recovery of patients having undergone major surgery.

106. A method according to claim 51 wherein the method is for accelerating bone fracture repair.

15 107. A method for increasing muscle mass, which method comprises administering to a human or other animal in need of such treatment an amount of a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

20 108. A method for the treatment of osteoporosis according to claim 53 wherein the bisphosphonate compound is ibandronate.

25 109. A method according to claim 59 wherein the estrogen agonist or antagonist is *cis*-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; (-)-*cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; *cis*-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; *cis*-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-naphthalene; 1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline; *cis*-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol; or 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydro-isoquinoline.

30 110. A method for promoting growth in growth hormone deficient children which comprises administering to a growth hormone deficient child a compound of claim 1 which is effective in promoting release of endogenous growth hormone.

International Application No
PCT/IB 96/01353

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/06 C07D471/04 C07D521/00 A61K38/05 A61K31/395

B. FIELDS SEARCHED

IPC 6 C07K C07D A61K

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TETRAHEDRON, vol. 50, no. 2, 1994, pages 515-528, XP0000652008 MORENO-MANAS, M. ET AL.: "Palladium-catalyzed allylation of 3-hydroxyisoxazole, 6-isoxazolone and 5-pyrazolone systems" cited in the application * schemes 1 and 2 *	61,67
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

*T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

*Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & document member of the same patent family

Date of the actual completion of the international search

18 March 1997

Date of mailing of the international search report

08.04.97

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INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/IB 96/01353

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DE 22 21 808 A (SANDOZ AG) 16 November 1972</p> <p>* pages 7,8,61: formula VIII *</p> <p>-----</p>	61,67

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